

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 November 2004 (04.11.2004)

PCT

(10) International Publication Number
WO 2004/094671 A2

(51) International Patent Classification⁷: C12Q 1/68

(21) International Application Number:
PCT/US2004/012788

(22) International Filing Date: 22 April 2004 (22.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/464,586 22 April 2003 (22.04.2003) US
60/464,588 22 April 2003 (22.04.2003) US

(71) Applicants (for all designated States except US): COLEY PHARMACEUTICAL GmbH [DE/DE]; Elisabeth-Selbert-Strasse 9, D-40764 Langenfeld (DE). COLEY PHARMACEUTICAL GROUP, INC. [US/US]; 93 Worcester Street, Suite 101, Wellesley, MA 02481 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VOLLMER, Jörg [DE/DE]; Kohlrauschweg 24, D-40591 Duesseldorf (DE).

JURK, Marion [DE/DE]; Klosterstr. 4, D-41540 Dornagel (DE). LIPFORD, Grayson, B. [GB/US]; 38 Bates Road, Watertown, MA 02472 (US). SCHETTER, Christian [DE/DE]; Oerkhaushof 35, D-40723 Hilden (DE). FORSBACH, Alexandra [DE/DE]; Raiffeisenstrasse N°1, D-40764 Rantingen (DE). KRIEG, Arthur, M. [US/US]; 173 Winding River Road, Wellesley, MA 02482 (US).

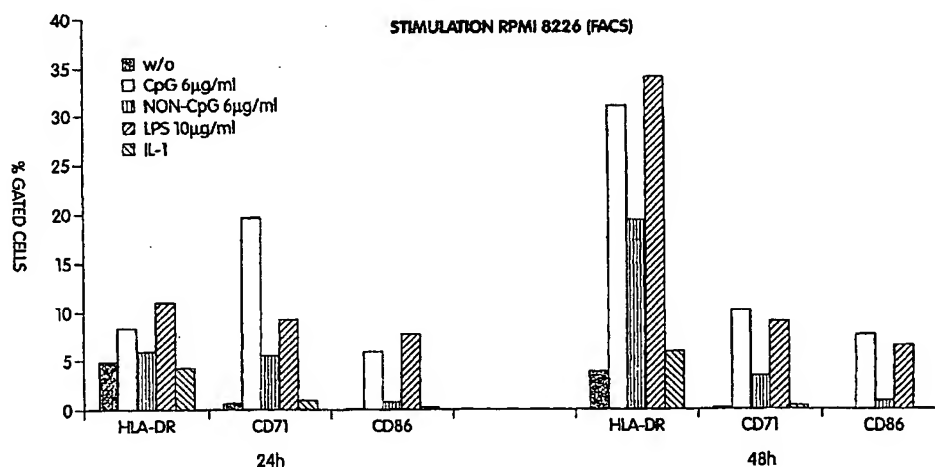
(74) Agent: TREVISAN, Maria, A.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

[Continued on next page]

(54) Title: METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT OF TLR LIGANDS



(57) Abstract: The invention provides in part novel screening methods and compositions for identifying and distinguishing between candidate immunomodulatory compounds. The invention further provides methods for assessing biological activity of composition containing a known TLR ligand. These latter methods can be used for quality assessment and selection of various lots of test compositions, including pharmaceutical products for clinical use.

WO 2004/094671 A2



GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

- 1 -

**METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT
OF TLR LIGANDS**

Background of the Invention

5 Nucleic acids with immunostimulatory activity have been identified. The first recognized immunostimulatory motif was the CpG motif in which at least the C of the dinucleotide was unmethylated. It has been postulated that mammalian subjects recognize the unmethylated dinucleotide as being of bacterial origin, and thus mount a heightened immune response following exposure. The ensuing immune response includes both cell mediated and
10 humoral aspects. Since the discovery of the CpG immunostimulatory motif, other immunostimulatory motifs have also been identified including the poly-T and T-rich motifs, the TG motif and the poly-G motif. In some instances, immunostimulation has also been observed in response to exposure to methylated CpG motifs and motif-less nucleic acids having phosphorothioate backbone linkages.

15 The responses induced by immunostimulatory nucleic acids are varied and can include production and secretion of cytokines, chemokines, and other growth factors. The nucleic acids can induce a heightened immune stimulation regardless of whether an antigen is also introduced to the subject. Identification of new motifs as well as of subtle differences between response profiles of different nucleic acids oftentimes can be laborious, and a high
20 throughput system for screening nucleic acids for their ability to be immunostimulatory as well as to determine the profile of responses they induce would be useful.

Summary of the Invention

 The invention provides in its broadest sense screening methods and tools for
25 identification and discrimination of immunomodulatory molecules and assessment and standardization of samples containing known immunomodulatory molecules. The immunomodulatory molecules can be immunostimulatory or immunoinhibitory, and most preferably are Toll-like receptor (TLR) ligands.

 In one aspect, the invention provides a screening method for identifying TLR agonists.
30 The method comprises contacting a cell line endogenously expressing at least one TLR with a test compound and measuring a test level of TLR signaling activity, wherein a positive test level is indicative of a TLR agonist (i.e., an immunostimulatory compound). The positive test

- 2 -

level may be apparent without referring to a control. Preferably, however, it is determined relative to a control (i.e., the TLR signaling activity from a reference compound).

In some embodiments, the reference compound is a compound that induces no response (i.e., a zero response) or a minimal response. In this case, a test level that is greater
5 than the reference level is indicative of a compound with TLR signaling activity. More preferably, the reference compound is a compound that induces a positive response (i.e., a non-zero response) and that is immunostimulatory. These reference compounds are referred to herein as negative and positive reference compounds, respectively. If the reference compound is immunostimulatory (i.e., a positive reference compound), a non-zero test level
10 that is lower than the reference level is still indicative of an immunostimulatory test compound. In this latter embodiment, the test compound is less immunostimulatory than the reference compound (for that particular readout), but it is nonetheless immunostimulatory given the non-zero response induced. There may be one or more concurrent or consecutive assays with a negative reference compound, a positive reference compound, or both. The
15 reference may also be a standard curve or data generated previously.

In a related aspect, the screening method involves exposing the same cell to a positive reference compound and a test compound in order to identify a test compound that inhibits the immunostimulatory response of the positive reference compound (i.e., a TLR antagonist or an immunoinhibitory compound).

20 In still a related aspect, the screening method involves exposing the same cells to a positive reference compound and a test compound in order to identify a test compound that enhances the immunostimulatory response of the positive reference compound (i.e., an enhancer).

In both of these latter aspects, the assay requires a co-incubation of the positive
25 reference compound, the test compound and the cells. Separate assays with positive reference compound alone and optionally negative reference compound alone are usually also performed.

The positive reference compound is a known TLR ligand. Non-limiting examples include but are not limited to TLR3 ligands, TLR7 ligands, TLR8 ligands and TLR9 ligands.
30 In some embodiments, the positive reference compound is an immunostimulatory nucleic acid. In some embodiments, the positive reference compound is a CpG nucleic acid, a poly-T nucleic acid, a T-rich nucleic acid or a poly-G nucleic acid. Another example of a positive

reference compound is a nucleic acid comprising a backbone that contains at least one phosphorothioate linkage.

It has been further discovered according to the invention that the RPMI 8226 cell line expresses TLR7 and responds to the imidazoquinoline compound R-848 (Resiquimod) which is known to signal through TLR7 and TLR8. Accordingly, the screening method can be performed using RPMI 8226, Raji or RAMOS cells and an imidazoquinoline compound such as R-848 or R-847 (Imiquimod) as the positive reference compound.

In one embodiment, the test compound is a nucleic acid such as but not limited to a DNA, an RNA and a DNA/RNA hybrid. The test compound may be a nucleic acid that does not comprise motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif. The test compound may be a nucleic acid that comprises a phosphorothioate backbone linkage. In another embodiment, the test compound is a non-nucleic acid small molecule. The non-nucleic acid small molecule may be derived from a molecular library. In other embodiments, the test compound comprises amino acids, carbohydrates such as polysaccharides. It may be a hormone or a lipid or contain moieties derived therefrom. In other embodiments, the test compounds are putative ligands for TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10 or TLR11.

In one embodiment, the cell is a RPMI 8226 cell, a Raji cell, a RAMOS cell, a THP-1 cells, a Nalm cell or a KG-1 cell and the TLR is TLR9. In another embodiment, the cell is a RPMI 8226 cell, a Raji cell or a RAMOS cell and the TLR is TLR7. In yet another embodiment, the cell is a KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell and the TLR is TLR3.

In another embodiment, the cell is an RPMI 8226 cell and the TLR is TLR7 or TLR9. In still another embodiment, the cell is a Raji cell and the TLR is TLR9, TLR7 or TLR3.

Depending upon the embodiment, the TLR signaling activity may be measured or detected in a number of ways. In one embodiment, the TLR signaling activity is measured by cytokine, chemokine, or growth factor secretion. The cytokine secretion may be selected from the group consisting of IL-6 secretion, IL-10 secretion, IL-12 secretion, IFN- α secretion and TNF- α secretion, but is not so limited. The chemokine secretion may be IP-10 secretion or IL-8 secretion, but is not so limited.

In another embodiment, the TLR signaling activity is measured by antibody secretion. The antibody secretion may be IgM secretion, but is not limited to this antibody subtype.

- 4 -

In another embodiment, the TLR signaling activity is measured by phosphorylation. The total level of phosphorylation in the cell or the level of phosphorylation of particular factors in the cell may be measured. These factors are preferably signaling factors and can be selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, Jun, c-fos, and subunits of NF- κ B, but are not so limited.

In still a further embodiment, the TLR signaling activity is measured by cell surface marker expression. In one embodiment, the TLR signaling activity is measured by an increase in cell surface marker expression. Examples of cell surface markers to be analyzed include CD71, CD86, HLA-DR, CD80, HLA Class I, CD54 and CD69. In other embodiments, the TLR signaling activity is measured by a decrease in cell surface marker expression. Cell surface marker expression can be determined using flow cytometry. TLR signaling activity can also be measured by protein production (e.g., by Western blot).

In another embodiment, the TLR signaling activity is measured by gene expression. Gene expression profiles may be determined using Northern blot analysis or RT-PCR that uses mRNA or total RNA as a starting material. The gene expression of interest may be that of the chemokines and cytokines and cell surface molecules recited above. Gene expression analysis can be performed using microarray techniques.

In yet another embodiment, the TLR signaling activity is measured by cell proliferation. Cell proliferation assays can be measured in a number of ways including but not limited to ^3H -thymidine incorporation.

In one embodiment, the cell is an RPMI 8226 cell and TLR signaling is indicated by expression of a marker such as CD71, CD86 and/or HLA-DR or by expression, production or secretion of a factor such as IL-8, IL-10, IP-10 and/or TNF- α . Preferably, in this latter embodiment, the RPMI 8226 cell is unmodified. In another embodiment, the cell is a Raji cell and the TLR signaling is indicated by IL-6 or IFN- α 2 expression, production or secretion. In yet another embodiment, the cell is a RAMOS cell and the TLR signaling is indicated by CD80 cell surface expression.

TLR signaling activity can be measured via a native readout or an artificial readout or both. A native readout is one that does not rely on introduction of a reporter construct into the cell of interest.

The cell line may be used in a modified or unmodified form. In one embodiment, the cell line is transfected with a reporter construct. The transfection may be transient or stable. The reporter construct generally comprises a promoter, a coding sequence and a

- 5 -

polyadenylation signal. The coding sequence may comprise a reporter sequence selected from the group consisting of an enzyme (e.g., luciferase, alkaline phosphatase, β -galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein (GFP, U.S. Patent No. 5,491,084), etc.), a surface-expressed molecule (e.g., CD25), a secreted molecule (e.g., IL-8, IL-12 p40, TNF- α , etc.), and other detectable protein sequences known to those of skill in the art. Preferably, the coding sequence encodes a protein, the level or activity of which can be quantified, with preferably a wide linear range.

In some embodiments, the promoter is a promoter that is responsive to TLR signaling pathways (i.e., a "TLR responsive promoter"). In some embodiments, the promoter contains a binding site for a transcription factor activated upon CpG nucleic acid exposure, such as for example NF- κ B. In other embodiments, the promoter contains a binding site for a transcription factor that is activated by a positive reference compound other than CpG nucleic acids. The transcription factor binding site may be selected from the group consisting of a NF- κ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE, as well as others known to those of skill in the art.

In another embodiment, the promoter contains a functional promoter element from an IL-1 gene, an IL-6 gene, an IL-8 gene, an IL-10 gene, an IL-12 p40 gene, an IFN- α 1 gene, an IFN- α 4 gene, an IFN- β gene, an IFN- γ gene, a TNF- α gene, a TNF- β gene, an IP-9 gene, an IP-10 gene, a RANTES gene, an ITAC gene, a MCP-1 gene, an IGFBP4 gene, a CD54 gene, a CD69 gene, a CD71 gene, a CD80 gene, a CD86 gene, a HLA-DR gene, and a HLA class I gene.

The TLR responsive promoter may be a TLR1 responsive promoter, a TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter, a TLR10 responsive promoter or a TLR11 responsive promoter.

In these latter embodiments, the cell line may be transfected with a reporter construct having a promoter derived from a particular cytokine, chemokine, or cell surface marker, and a unique reporter coding sequence conjugated thereto. In this way, the readout from a particular reporter construct is a surrogate readout for cytokine, chemokine, or cell surface marker readout. Measuring readout from the reporter coding sequences described herein is in

some instances easier than measuring cytokine or chemokine secretion, or upregulation of a cell surface marker.

In these latter embodiments, the cell line may be transfected with a number of reporter constructs each having a promoter derived from a particular cytokine, chemokine, or cell surface marker, and a unique distinguishable coding sequence conjugated thereto. In these
5 embodiments, multiple readouts are possible from one screen. In other embodiments, multiple native readouts are also possible from one screen.

In a related embodiment, the cell may be further transfected with a nucleic acid that codes for a TLR polypeptide or a fragment thereof. Preferably, the TLR is one that is not
10 endogenously expressed by the cell. As an example, if the cell is an RPMI 8226 cell which has been shown to express TLR7 and TLR9 according to the invention, then it may be modified to express TLRs other than these (e.g., TLR8) in some embodiments. In this aspect, the RPMI 8226 cell is responsive to TLR8 ligands. In preferred embodiments, the TLR is a human TLR (i.e., hTLR).

In another aspect, the invention provides an RPMI 8226 cell transfected with a TLR
15 nucleic acid. In still another embodiment, the TLR nucleic acid is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR8, TLR10 and TLR11. The encoded TLRs nucleic acids can derive from human or non-human sources. Examples of non-human sources include, but are not limited to, murine, bovine, canine, feline, ovine,
20 porcine, and equine species. Other species include chicken and fish, e.g., aquaculture species. The TLR nucleic acids can also include chimeric sequences consisting of domains originating from different species. In preferred embodiments, the TLR is a human TLR.

In still another aspect, the invention provides kits including the cells lines (e.g., the RPMI 8226 cell line), the reporter constructs and/or expression constructs described above,
25 and instructions for use.

Other aspects of the invention provide methods for analyzing the biological activity of individual lots of material containing previously identified specific TLR ligands (i.e., specific compounds which are ligands for a particular TLR) intended for use as, or for use in the preparation of, pharmaceutical compositions. The methods permit a qualitative and,
30 importantly, a quantitative assessment of biological activity of individual lots of TLR ligands, pre-formulation as well as post-formulation. Such methods are useful in the manufacture and validation of pharmaceutical compositions containing, as an active agent, at least one specific ligand of at least one specific TLR. The specific TLR can be any known TLR, including

- 7 -

without limitation TLR3, TLR7, TLR8 and TLR9. The specific TLR ligand is an isolated TLR ligand, either found in nature or synthetic (not found in nature), including in particular certain nucleic acid molecules and small molecules. Nucleic acid molecules that are specific TLR ligands include synthetic and naturally-occurring oligonucleotides having specific base
5 sequence motifs. Furthermore, specific TLR ligands include both agonists and antagonists of specific TLR.

These methods are to be distinguished from test procedures and acceptance criteria for new drug substances and new drug products which are classified as chemical substances. Unlike the afore-mentioned test procedures and acceptance criteria, the methods of the instant
10 invention deal specifically with characterizing drug substances and drug products which are classified as oligonucleotides. Oligonucleotides are explicitly excluded in ICH Topic Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 – Consensus Guideline: 6 October 1999, § 1.3.

Further still, the methods of the instant invention are to be distinguished from test
15 procedures and acceptance criteria for biotechnological/biological products. Unlike the afore-mentioned test procedures and acceptance criteria, the methods of the invention deal specifically with characterizing biotechnological/biological products which are classified as DNA products. DNA products are explicitly excluded in ICH Harmonised Tripartite Guideline Specifications: Test Procedures and Acceptance Criteria for
20 Biotechnological/Biological Products, Step 4 – 10 March 1999, § 1.3.

In one aspect, the invention provides a method for quality assessment of a test composition containing a known TLR ligand. The method according to this aspect of the invention involves measuring a reference activity of a reference composition comprising a known TLR ligand, wherein the known TLR ligand is a nucleic acid molecule; measuring a
25 test activity of a test composition comprising the known TLR ligand; and comparing the test activity to the reference activity. In one embodiment the method further involves the step of selecting the test composition if the test activity falls within a predetermined range of variance about the reference activity.

In one embodiment, the reference composition is a first production lot of a
30 pharmaceutical composition comprising the known TLR ligand, and the test composition is a second production lot of a pharmaceutical composition comprising the known TLR ligand. This embodiment is particularly useful as a method for developing and applying acceptance criteria for finished pharmaceutical products containing a known TLR ligand.

In another embodiment, the reference composition is a first in-process lot of a composition comprising the known TLR ligand, and the test composition is a second in-process lot of a composition comprising the known TLR ligand. This embodiment is particularly useful as a method for developing and applying acceptance criteria for raw materials and/or other in-process materials containing a known TLR ligand bound for use in a pharmaceutical product.

In one embodiment according to this aspect of the invention, measuring the reference activity involves contacting the reference composition with an isolated cell expressing a TLR responsive to the known TLR ligand, and measuring the test activity involves contacting the test composition with the isolated cell expressing the TLR responsive to the known TLR ligand. Further, in one embodiment the isolated cell expressing the TLR responsive to the known TLR ligand includes an expression vector for the TLR responsive to the known TLR ligand. Such expression vector, and likewise for any expression vector according to the instant invention, can be introduced into the cell using any suitable method.

In one embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand naturally expresses the TLR responsive to the known TLR ligand. Such a cell can be naturally occurring or it can be a cell line, provided the cell does not include an expression vector introduced into the cell for the purpose of artificially inducing the cell to express or overexpress the TLR.

In one particular embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226. In another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is Raji, RAMOS, Nalm, THP-1 or KG-1 and the TLR is TLR9. In another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226, Raji or RAMOS and the TLR is TLR7. In yet another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is a KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a HeLa cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell and the TLR is TLR3.

Further according to this aspect of the invention, in one embodiment measuring the reference activity and measuring the test activity each comprises measuring signaling activity mediated by a TLR responsive to the known TLR ligand. As described in greater detail elsewhere herein, TLR signaling involves a series of intracellular signaling events. These signaling events give rise to various downstream products, including certain transcription

factors (e.g., NF- κ B and AP-1), cytokines, chemokines, etc., which can affect the activity of certain gene promoters. For example, in one embodiment the signaling activity is activity of a reporter gene or reporter construct under the control of a NF- κ B response element.

In other embodiments, the signaling activity is activity of a reporter gene or reporter
5 construct under the control of an interferon-stimulated response element (ISRE); an IFN- α promoter; an IFN- β promoter; an IL-6 promoter; an IL-8 promoter; an IL-12 p40 promoter; a RANTES promoter; an IL-10 promoter or an IP-10 promoter.

In one embodiment, the known TLR ligand is an immunostimulatory nucleic acid. An immunostimulatory nucleic acid can include, without limitation, a CpG nucleic acid. In
10 another embodiment, the known TLR ligand is an immunoinhibitory nucleic acid. When the known TLR ligand is a TLR antagonist (e.g., an immunoinhibitory oligonucleotide), the method according to this aspect of the invention can further involve measuring the reference activity of the reference composition and measuring the test activity of the test composition, each performed in the presence of a known immunostimulatory TLR ligand.

15 In various embodiments, the known TLR ligand is a ligand for a particular TLR. Thus in one embodiment the known TLR ligand is a TLR9 ligand. More specifically, in one embodiment the known TLR ligand is a CpG nucleic acid.

In one embodiment, the known TLR ligand is a TLR3 ligand. Such a ligand can include, for example, a double-stranded RNA or a homolog thereof.

20 In one embodiment, the known TLR ligand is a TLR7 ligand. In one embodiment the known TLR ligand is a TLR8 ligand.

The invention provides in another aspect a method for quality assessment of a test lot of a pharmaceutical product containing a known TLR9 ligand. The method according to this aspect of the invention involves measuring a reference activity of a reference lot of a
25 pharmaceutical product comprising a known TLR9 ligand, wherein the known TLR9 ligand is a nucleic acid molecule; measuring a test activity of a test lot of a pharmaceutical product comprising the known TLR9 ligand; comparing the test activity to the reference activity; and rejecting the test lot if the test activity falls outside of a predetermined range of variance about the reference activity.

30 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGT CGT TTT GTC GTT-3' (SEQ ID NO:1).

- 10 -

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGA CGT TTT GTC GTT-3' (SEQ ID NO:139).

5 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGT CGT TTT TTT CGA-3' (SEQ ID NO:140).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT CGT CGT TTC GTC GTT-3' (SEQ ID NO:141).

10 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT CGT CGT TTT GTC GTT-3' (SEQ ID NO:142).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TTC GGT CGT TTT-3' (SEQ ID NO:143).

15 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TTC GTG CGT TTT T-3' (SEQ ID NO:144).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TCG GCG GCC GCC G-3' (SEQ ID NO:145).

20 In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TC_G TTT TAC_GGC GCC_GTG CCG-3' (SEQ ID NO:146), wherein every internucleoside linkage is
25 phosphorothioate except for those indicated by “_”, which are phosphodiester.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention.

30

Brief Description of the Figures

- 11 -

Fig. 1 is a bar graph showing cell surface expression of various markers by RPMI 8226 24 hours and 48 hours following stimulation with CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), LPS and IL-1.

Fig. 2 is a bar graph showing IL-8 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 3 is a bar graph showing IL-6 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 4 is a bar graph showing IP-10 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 5 is a bar graph showing IL-10 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 6 is a dose response curve showing fold induction of IL-8 production 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1) and non-CpG nucleic acid (SEQ ID NO: 2). The EC₅₀ for CpG nucleic acid is 19 nM and the EC₅₀ for non-CpG nucleic acid is 263 nM.

Fig. 7 is a bar graph showing NF- κ B activation in RPMI 8226 transfected transiently with a NF- κ B-luciferase reporter gene construct as a function of cell density and nucleic acid amount transfected, following exposure to CpG nucleic acid (SEQ ID NO: 1), LPS and TNF- α . NF- κ B activation is measured by luciferase activity.

Fig. 8 is a bar graph showing RT-PCR results from RNA isolated from RPMI 8226 using gene specific primers for TLR7, TLR8 and TLR9 genes.

Fig. 9 is a dose response curve showing IP-10 production induced by SEQ ID NO: 1, and inhibition thereof in the presence of SEQ ID NO: 151, a immunoinhibitory nucleic acid.

Fig. 10 is a bar graph showing the results of a TLR9 RT-PCR analysis of a number of cell lines.

Fig. 11 is a bar graph showing the results of a TLR7 RT-PCR analysis of a number of cell lines.

Fig. 12 is a bar graph showing the results of a TLR3 RT-PCR analysis of a number of cell lines.

Fig. 13 is a bar graph showing the results of a TLR3, TLR7, TLR8 and TLR9 RT-PCR analysis of the Raji cell line.

Fig. 14 is a graph showing IL-6 production by the Raji cell line upon stimulation with various ODN (SEQ ID NO:1; SEQ ID NO:154; SEQ ID NO:158; SEQ ID NO:160; SEQ ID
5 NO:159; SEQ ID NO:161).

Fig. 15 is a bar graph showing IL-6 production of the Raji cell line upon stimulation with poly I:C and R-848.

Fig. 16 is a bar graph showing IFN- α 2 production by the Raji cell line upon stimulation with CpG ODN (SEQ ID NO: 1), R-848 and poly I:C.

Fig. 17 is a bar graph showing CD80 expression (by flow cytometry) by the RAMOS
10 cell line upon stimulation with CpG ODN (SEQ ID NO: 1) and non-CpG ODN (SEQ ID NO: 2).

Fig. 18A is a bar graph showing the induction of NF- κ B by 293 fibroblast cells transfected with human TLR9 in response to exposure to various stimuli, including CpG-
15 ODN, GpC-ODN, LPS, and medium.

Fig. 18B is a bar graph showing the amount of IL-8 produced by 293 fibroblast cells transfected with human TLR9 in response to exposure to various stimuli, including CpG-ODN, GpC-ODN, LPS, and medium.

Fig. 19 is a bar graph showing the induction of NF- κ B-luc produced by stably
20 transfected 293-mTLR9 cells in response to exposure to various stimuli, including CpG-ODN, methylated CpG-ODN (Me-CpG-ODN), GpC-ODN, LPS and medium.

Fig. 20 is a bar graph showing the induction of NF- κ B-luc produced by stably transfected 293-hTLR9 cells in response to exposure to various stimuli, including CpG-ODN, methylated CpG-ODN (Me-CpG-ODN), GpC-ODN, LPS and medium.

Fig. 21 is a series of gel images depicting the results of reverse transcriptase-
25 polymerase chain reaction (RT-PCR) assays for murine TLR9 (mTLR9), human TLR9 (hTLR9), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in untransfected control 293 cells, 293 cells transfected with mTLR9 (293-mTLR9), and 293 cells transfected with hTLR9 (293-hTLR9).

30

It is to be understood that the Figures are not required for enablement of the invention.

Brief Description of Sequences

SEQ ID NO:1 is the nucleotide sequence of an immunostimulatory nucleic acid (TLR9 ligand).

SEQ ID NO:2 is the nucleotide sequence of a non-CpG nucleic acid.

SEQ ID NO:3 is the nucleotide sequence of human TLR2 cDNA (U88878).

5 SEQ ID NO:4 is the amino acid sequence of human TLR2 protein (AAC34133).

SEQ ID NO:5 is the nucleotide sequence of murine TLR2 cDNA (AF165189).

SEQ ID NO:6 is the amino acid sequence of murine TLR2 protein (NP_036035).

SEQ ID NO:7 is the nucleotide sequence of human TLR3 cDNA (NM_003265).

SEQ ID NO:8 is the amino acid sequence of human TLR3 protein (NP_003256).

10 SEQ ID NO:9 is the nucleotide sequence of murine TLR3 cDNA (AF355152).

SEQ ID NO:10 is the amino acid sequence of murine TLR3 protein (AAK26117).

SEQ ID NO:11 is the nucleotide sequence of human TLR4 cDNA (U88880).

SEQ ID NO:12 is the nucleotide sequence of human TLR4 cDNA transcript variant 4 (NM_138557).

15 SEQ ID NO:13 is the nucleotide sequence of human TLR4 cDNA transcript variant 2 (NM_138556).

SEQ ID NO:14 is the nucleotide sequence of human TLR4 cDNA transcript variant 1 (NM_138554).

20 SEQ ID NO:15 is the nucleotide sequence of human TLR4 cDNA transcript variant 3 (NM_003266).

SEQ ID NO:16 is the amino acid sequence of human TLR4 protein isoform A (NP_612564).

SEQ ID NO:17 is the amino acid sequence of human TLR4 protein isoform B (NP_612566).

25 SEQ ID NO:18 is the amino acid sequence of human TLR4 protein isoform C (NP_003257).

SEQ ID NO:19 is the amino acid sequence of human TLR4 protein isoform D (NP_612567).

SEQ ID NO:20 is the nucleotide sequence of murine TLR4 cDNA (NM_021297).

30 SEQ ID NO:21 is the nucleotide sequence of murine TLR4 mRNA (AF185285).

SEQ ID NO:22 is the nucleotide sequence of murine TLR4 mRNA (AF110133).

SEQ ID NO:23 is the amino acid sequence of murine TLR4 protein (AAD29272).

SEQ ID NO:24 is the amino acid sequence of murine TLR4 protein (AAF04278).

- SEQ ID NO:25 is the nucleotide sequence of human TLR5 cDNA (AB060695).
SEQ ID NO:26 is the amino acid sequence of human TLR5 protein (BAB43558).
SEQ ID NO:27 is the amino acid sequence of human TLR5 protein (O60602).
SEQ ID NO:28 is the amino acid sequence of human TLR5 protein (AAC34136).
5 SEQ ID NO:29 is the nucleotide sequence of murine TLR5 cDNA (AF186107).
SEQ ID NO:30 is the amino acid sequence of murine TLR5 protein (AAF65625).
SEQ ID NO:31 is the nucleotide sequence of human TLR7 cDNA (AF240467).
SEQ ID NO:32 is the nucleotide sequence of human TLR7 cDNA (AF245702).
SEQ ID NO:33 is the nucleotide sequence of human TLR7 cDNA (NM_016562).
10 SEQ ID NO:34 is the amino acid sequence of human TLR7 protein (AAF60188).
SEQ ID NO:35 is the amino acid sequence of human TLR7 protein (AAF78035).
SEQ ID NO:36 is the amino acid sequence of human TLR7 protein (NP_057646).
SEQ ID NO:37 is the amino acid sequence of human TLR7 protein (Q9NYK1).
SEQ ID NO:38 is the nucleotide sequence of murine TLR7 cDNA (AY035889).
15 SEQ ID NO:39 is the nucleotide sequence of murine TLR7 splice variant
(NM_133211).
SEQ ID NO:40 is the nucleotide sequence of murine TLR7 splice variant (AF334942).
SEQ ID NO:41 is the amino acid sequence of murine TLR7 protein (AAK62676).
SEQ ID NO:42 is the amino acid sequence of murine TLR7 protein (AAL73191).
20 SEQ ID NO:43 is the amino acid sequence of murine TLR7 protein (AAL73192).
SEQ ID NO:44 is the amino acid sequence of murine TLR7 protein (NP_573474).
SEQ ID NO:45 is the amino acid sequence of murine TLR7 protein (P58681).
SEQ ID NO:46 is the nucleotide sequence of human TLR8 cDNA (AF245703).
SEQ ID NO:47 is the nucleotide sequence of human TLR8 cDNA (AF246971).
25 SEQ ID NO:48 is the nucleotide sequence of human TLR8 cDNA (NM_138636).
SEQ ID NO:49 is the nucleotide sequence of human TLR8 cDNA (NM_016610).
SEQ ID NO:50 is the amino acid sequence of human TLR8 protein (AAF78036).
SEQ ID NO:51 is the amino acid sequence of human TLR8 protein (AAF64061).
SEQ ID NO:52 is the amino acid sequence of human TLR8 protein (Q9NR97).
30 SEQ ID NO:53 is the amino acid sequence of human TLR8 protein (NP_619542).
SEQ ID NO:54 is the amino acid sequence of human TLR8 protein (NP_057694).
SEQ ID NO:55 is the nucleotide sequence of murine TLR8 cDNA (AY035890).
SEQ ID NO:56 is the nucleotide sequence of murine TLR8 cDNA (NM_133212).

- 15 -

- SEQ ID NO:57 is the amino acid sequence of murine TLR8 protein (AAK62677).
SEQ ID NO:58 is the amino acid sequence of murine TLR8 protein (NP_573475).
SEQ ID NO:59 is the amino acid sequence of murine TLR8 protein (P58682).
SEQ ID NO:60 is the nucleotide sequence of human TLR9 cDNA (AF245704).
5 SEQ ID NO:61 is the nucleotide sequence of human TLR9 cDNA (AB045180).
SEQ ID NO:62 is the amino acid sequence of human TLR9 protein (AAF78037).
SEQ ID NO:63 is the amino acid sequence of human TLR9 protein (AAF72189).
SEQ ID NO:64 is the amino acid sequence of human TLR9 protein (AAG01734).
SEQ ID NO:65 is the amino acid sequence of human TLR9 protein (AAG01735).
10 SEQ ID NO:66 is the amino acid sequence of human TLR9 protein (AAG01736).
SEQ ID NO:67 is the amino acid sequence of human TLR9 protein (BAB19259).
SEQ ID NO:68 is the nucleotide sequence of murine TLR9 cDNA (AF348140).
SEQ ID NO:69 is the nucleotide sequence of murine TLR9 cDNA (AB045181).
SEQ ID NO:70 is the nucleotide sequence of murine TLR9 cDNA (AF314224).
15 SEQ ID NO:71 is the nucleotide sequence of murine TLR9 cDNA (NM_031178).
SEQ ID NO:72 is the amino acid sequence of murine TLR9 protein (AAK29625).
SEQ ID NO:73 is the amino acid sequence of murine TLR9 protein (AAK28488).
SEQ ID NO:74 is the amino acid sequence of murine TLR9 protein (BAB19260).
SEQ ID NO:75 is the amino acid sequence of murine TLR9 protein (NP_112455).
20 SEQ ID NO:76 is the nucleotide sequence of human TLR10 cDNA (AF296673).
SEQ ID NO:77 is the amino acid sequence of human TLR10 protein (AAK26744).
SEQ ID NO:78 is the nucleotide sequence of human TLR6 cDNA (AB020807).
SEQ ID NO:79 is the nucleotide sequence of human TLR6 mRNA (NM_006068).
SEQ ID NO:80 is the amino acid sequence of human TLR6 protein (BAA78631).
25 SEQ ID NO:81 is the amino acid sequence of human TLR6 protein (NP_006059).
SEQ ID NO:82 is the amino acid sequence of human TLR6 protein (Q9Y2C9).
SEQ ID NO:83 is the nucleotide sequence of murine TLR6 cDNA (AB020808).
SEQ ID NO:84 is the nucleotide sequence of murine TLR6 cDNA (NM_011604).
SEQ ID NO:85 is the nucleotide sequence of murine TLR6 cDNA (AF314636).
30 SEQ ID NO:86 is the amino acid sequence of murine TLR6 protein (BAA78632).
SEQ ID NO:87 is the amino acid sequence of murine TLR6 protein (AAG38563).
SEQ ID NO:88 is the amino acid sequence of murine TLR6 protein (NP_035734).
SEQ ID NO:89 is the amino acid sequence of murine TLR6 protein (Q9EPW9).

- 16 -

SEQ ID NO:90 is the nucleotide sequence of a consensus sequence for NF- κ B p50 subunit.

SEQ ID NO:91 is the nucleotide sequence of a consensus sequence for NF- κ B p65 subunit.

5 SEQ ID NO:92 is the nucleotide sequence of an example of an NF- κ B p65 subunit binding site.

SEQ ID NO:93 is the nucleotide sequence of an example of a murine CREB binding site.

10 SEQ ID NO:94 is the nucleotide sequence of an example of a murine AP-1 binding site.

SEQ ID NO:95 is the nucleotide sequence of an example of a murine AP-1 binding site.

SEQ ID NO:96 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:97 is the nucleotide sequence of an example of an ISRE.

15 SEQ ID NO:98 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:99 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:100 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:101 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:102 is the nucleotide sequence of an example of an ISRE.

20 SEQ ID NO:103 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:104 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:105 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:106 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:107 is the nucleotide sequence of an example of an NFAT binding site.

25 SEQ ID NO:108 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:109 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:110 is the nucleotide sequence of an example of a GAS.

SEQ ID NO:111 is the nucleotide sequence of a p53 binding site consensus sequence.

SEQ ID NO:112 is the nucleotide sequence of an example of a p53 binding site.

30 SEQ ID NO:113 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:114 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:115 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:116 is the nucleotide sequence of an example of a p53 binding site.

- 17 -

SEQ ID NO:117 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:118 is the nucleotide sequence of an example of a TARE (TNF- α response element).

SEQ ID NO:119 is the nucleotide sequence of an example of an SRF binding site.

5 SEQ ID NO:120 is the nucleotide sequence of an example of an SRF binding site.

SEQ ID NO:121 is the nucleotide sequence of the -620 to +50 promoter region of IFN- α 4.

SEQ ID NO:122 is the nucleotide sequence of the -140 to +9 promoter region of IFN- α 1.

10 SEQ ID NO:123 is the nucleotide sequence of the -140 to +9 promoter region of IFN- α 1 (point mutation, AL353732).

SEQ ID NO:124 is the nucleotide sequence of the -280 to +20 promoter region of IFN- β .

15 SEQ ID NO:125 is the nucleotide sequence of the -397 to +5 promoter region of human RANTES (AB023652).

SEQ ID NO:126 is the nucleotide sequence of the -751 to +30 promoter region of human IL-12 p40.

SEQ ID NO:127 is the nucleotide sequence of the -250 to +30 promoter region of human IL-12 p40.

20 SEQ ID NO:128 is the nucleotide sequence of the -288 to +7 promoter region of human IL-6.

SEQ ID NO:129 is the nucleotide sequence of the IL-6 gene promoter from -1174 to +7 (M22111).

25 SEQ ID NO:130 is the nucleotide sequence of the -734 to +44 promoter region derived from human IL-8.

SEQ ID NO:131 is the nucleotide sequence of the -162 to 44 promoter region of human IL-8.

SEQ ID NO:132 is the nucleotide sequence of the -615 to +30 promoter region of human TNF- α .

30 SEQ ID NO:133 is the nucleotide sequence of a promoter region of human TNF- β .

SEQ ID NO:134 is the nucleotide sequence of the -875 to +97 promoter region of human IP-10.

- 18 -

SEQ ID NO:135 is the nucleotide sequence of the -219 to +114 promoter region of human CXCL11 (IP-9).

SEQ ID NO:136 is the nucleotide sequence of the full length promoter region of human CXCL11 (IP-9).

5 SEQ ID NO:137 is the nucleotide sequence of the -289 to +217 promoter region of IGFBP4 (Insulin growth factor binding protein 4).

SEQ ID NO:138 is the nucleotide sequence of the full length promoter region of IGFBP4.

10 SEQ ID NO:139 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:140 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:141 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:142 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:143 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:144 is the nucleotide sequence of an immunostimulatory nucleic acid.
15 SEQ ID NO:145 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:146 is the nucleotide sequence of an immunostimulatory nucleic acid.
SEQ ID NO:147 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

20 SEQ ID NO:148 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:149 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:150 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

25 SEQ ID NO:151 is the nucleotide sequence of an immunoinhibitory nucleic acid.

SEQ ID NO:152 is the nucleotide sequence of a sense primer for human TLR3.

SEQ ID NO:153 is the nucleotide sequence of an antisense primer for human TLR3.

SEQ ID NO:154 is the nucleotide sequence of a GpC nucleic acid.

SEQ ID NO:155 is the nucleotide sequence of a CpG ODN.

30 SEQ ID NO:156 is the nucleotide sequence of a GpC ODN.

SEQ ID NO:157 is the nucleotide sequence of a Me-CpG ODN.

SEQ ID NO:158 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:159 is the nucleotide sequence of a TLR9 ligand.

- 19 -

SEQ ID NO:160 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:161 is the nucleotide sequence of a TLR9 ligand.

Detailed Description of the Invention

5 In its broadest sense, the invention relates to screening methods and tools to be used to identify and discriminate between newly discovered immunomodulatory molecules and to compare and standardize compositions of known immunomodulatory molecules. The immunomodulatory molecules are preferably TLR ligands.

10 Thus, the invention is based in part on the discovery that cell lines expressing endogenous TLR respond to TLR ligands in a manner similar to the response of peripheral blood mononuclear cells (PBMC). PBMC respond to immunomodulatory TLR ligands by modulating one or more parameters including gene expression, cell surface marker expression, cytokine and/or chemokine production and secretion, cell cycle status, phosphorylation status, and the like. TLR ligands can be categorized and distinguished based
15 on the cellular changes they induce (i.e., their induction profiles). The ability of a TLR ligand to provide therapeutic or prophylactic benefit to a subject depends on its induction profile. The ability to screen new TLR ligands for a panel of response indicators or parameters allows for rapid discrimination and categorization of TLR ligands. Moreover, the similarity between the cell line responses and those observed after in vivo administration of the TLR ligand
20 indicates that the cell lines are suitable predictors of in vivo activity. The use of in vitro propagated cell lines additionally overcomes the variability encountered when using freshly isolated PBMC.

The TLR ligands identified according to the invention therefore can be used therapeutically or prophylactically in a more patient- or disorder-specific manner. The
25 invention allows for the tailoring of TLR ligands for particular patients or disorders.

The invention identifies a number of cell lines that can be used to identify TLR ligands based on endogenous TLR expression such as TLR3, TLR7 and TLR9 expression. As an example, the invention is premised in part on the discovery of TLR9 expression in a number of cell lines including RPMI 8226, Raji, RAMOS, THP-1, Nalm-6 and KG-1. Cell lines
30 RPMI 8226, Raji and RAMOS have been determined to express TLR7 according to the invention. Cell lines KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a HeLa cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell have been discovered to express TLR3 according to the invention.

It is further premised in part on the discovery that RPMI 8226 cells respond to the imidazoquinoline compound R-848. Consistent with this latter finding, it was also discovered
5 that RPMI 8226 cells express TLR7.

The invention in other aspects provides for screening methods and tools for verifying and standardizing compositions containing known TLR ligands. These compositions may be for example commercial production lots to be used in a clinical setting. Accordingly, the invention provides methods for standardizing lots of known TLR ligands prior to distribution
10 and use clinically. In this way, production processes can be observed and controlled and substandard production lots can be identified and eliminated prior to shipment.

The methods of the instant invention can be used at any step in the preparation and production of clinical material, i.e., pharmaceutical product. In particular, the methods will find use in characterizing or validating raw materials, in-process materials, finished product
15 materials (e.g., pre-release materials), and post-production materials (e.g., post-release materials). The methods can also be used to validate existing process methods, as well as to validate new or changed process methods used in the production of the pharmaceutical product.

20 Screening Assays Generally

The screening assays provided herein may be used to identify immunomodulatory agents. Immunomodulatory agents are agents that either stimulate or inhibit immune responses in a subject. Accordingly, as used herein, immunomodulation embraces both immunostimulation and immunoinhibition.

25 The screening methods are used to identify TLR agonists and antagonists. The methods can also be used to identify compounds that enhance the immunostimulation induced by a TLR agonist. This latter set of compounds is referred to herein as "enhancers". A TLR agonist is a compound that stimulates TLR signaling activity. A TLR antagonist is a compound that inhibits TLR signaling activity. Agonists are generally referred to herein as
30 immunostimulatory compounds because stimulation of TLR is associated with immune stimulation. Antagonists are generally referred to herein as immunoinhibitory compounds because inhibition of TLR is associated with immune inhibition. TLR antagonists include compounds that reduce (or eliminate completely) the immunostimulation induced by a TLR

- 21 -

agonist. In some embodiments, the agonists, antagonists and enhancers are TLR ligands (i.e., they bind to a TLR). In other embodiments, the test compounds with agonist, antagonist or enhancer activity may act downstream or upstream of the TLR-TLR ligand interaction.

An "immunostimulatory compound" as used herein refers to a natural or synthetic compound that characteristically induces a TLR-mediated response when contacted with a suitable functional TLR polypeptide. In one embodiment the immunostimulatory compound is a natural or synthetic compound that induces a TLR-mediated response when contacted with a cell that naturally or artificially expresses a suitable functional TLR polypeptide. Depending on the aspect of the invention, the cell may be an experimental cell or a primary cell such as a PBMC.

Examples of immunostimulatory compounds include the following immunostimulatory nucleic acids, which are discussed in further detail below:

	5'-TCGTCGTTTTGTCGTTTTGTCGTT-3'	(SEQ ID NO:1)
	5'-TCGTCGTTTTGACGTTTTGTCGTT-3'	(SEQ ID NO:139)
15	5'-TCGTCGTTTTGTCGTTTTTTTCGA-3'	(SEQ ID NO:140)
	5'-TCGTCGTTTCGTCGTTTCGTCGTT-3'	(SEQ ID NO:141)
	5'-TCGTCGTTTCGTCGTTTGTGTCGTT-3'	(SEQ ID NO:142)
	5'-TCGTCGTTTTTCGGTCGTTTTT-3'	(SEQ ID NO:143)
	5'-TCGTCGTTTTTCGTGCGTTTTT-3'	(SEQ ID NO:144)
20	5'-TCGTCGTTTTTCGGCGGCCGCCG-3'	(SEQ ID NO:145)
	5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3'	(SEQ ID NO:146)

Imidazoquinolines are immune response modifiers thought to induce expression of several cytokines including interferons (e.g., IFN- α and IFN- β), TNF- α and some interleukins (e.g., IL-1, IL-6 and IL-12) as well as chemokines (e.g., IP-10 and IL-8). Imidazoquinolines are capable of stimulating a Th1 immune response, as evidenced in part by their ability to induce increases in IgG2a levels. Imidazoquinoline agents reportedly are also capable of inhibiting production of Th2 cytokines such as IL-4, IL-5, and IL-13. Some of the cytokines induced by imidazoquinolines are produced by macrophages and dendritic cells. Some species of imidazoquinolines have been reported to increase NK cell lytic activity and to stimulate B cells proliferation and differentiation, thereby inducing antibody production and secretion. Imidazoquinoline mimics can also be tested using the screening methods.

- 22 -

An "immunoinhibitory compound" as used herein refers to a natural or synthetic compound that characteristically inhibits a TLR-mediated response when contacted with a suitable functional TLR polypeptide. In one embodiment the immunoinhibitory compound is a natural or synthetic compound that inhibits a TLR-mediated response when contacted with a cell that naturally or artificially expresses a suitable functional TLR polypeptide.

In addition to the immunoinhibitory nucleic acids disclosed elsewhere herein, immunoinhibitory compounds and TLR antagonists encompass certain small molecules (chloroquine, quinacrine, 9-aminoacridines and 4-aminoquinolines, and derivatives thereof) described by Macfarlane and colleagues in U.S. Pat. 6,221,882; U.S. Pat. 6,399,630; U.S. Pat. 6,479,504; U.S. Pat. 6,521,637; and published U.S. Pat. application 2002/0151564, the contents of all of which are hereby incorporated by reference in their entirety.

The invention provides in part methods and tools that utilize cell lines, in modified or unmodified form, as surrogates for PBMC. Immunomodulation by TLR ligands can be assessed using one or preferably more parameters including but not limited to cytokine and chemokine secretion, upregulation of cell surface markers, changes in cell proliferation, phosphorylation changes, and the like. These parameters may be native readouts or artificial readouts as described herein.

The cellular response to immunostimulatory nucleic acids by the cell lines described herein (e.g., RPMI 8226, Raji, RAMOS, and the like) so resembles that of PBMC that these cells can be used to identify and differentiate between immunomodulatory compounds based on the extent of the induced response and the particular profile of that response. The invention provides a number of cell lines each with a particular endogenous TLR expression profile, as described herein.

The cell lines can be used to identify immunomodulatory compounds with particular response profiles. As an example, the cell lines can be used to identify molecules that are mimics to known TLR ligands. The cell lines can also be used to identify TLR ligands that trigger some but not necessarily all of the responses induced by known TLR ligands. For example, the cell line can be used to distinguish between compounds based on individual or group cytokine or chemokine secretion, or based on upregulation of one, a subset or all cell surface markers. As an example, in some therapeutic instances, it may be desirable to use a compound that induces the secretion of relatively high levels of chemokine such as IP-10, yet induces only relatively low levels of one or more other factors. The screening methods of the invention allow for the identification of such a compound with this type of induction profile.

- 23 -

It is to be understood that the screening method also can be used to determine effective amounts of known and newly identified immunomodulatory compounds. For example, the EC₅₀ value of a TLR ligand for the production of a particular cytokine or chemokine can be determined, thereby facilitating comparison between different nucleic acids.

5 Generally, these assays require the incubation of cells with a reference compound and a test compound, and an analysis of the readout. Depending on the embodiment, the same cells are exposed to the reference compound and the test compound. An example of this latter embodiment is a screening assay for compounds that enhance the immunostimulatory effects of a TLR agonist. Another example is a screening assay for compounds that inhibit the
10 immunostimulatory effects of a TLR agonist. In both examples, the reference compound is a positive reference compound (i.e., it is itself immunostimulatory).

In other embodiments, particularly those directed at identifying immunostimulatory compounds, separate aliquots from the same cell line (or from the same freshly harvested cell population) are exposed to either the reference compound or the test compound, and the
15 readouts from each are measured and compared to the other. If the reference compound is a negative reference compound (i.e., it is inert and neither immunostimulatory nor immunoinhibitory), then any test level that is greater than the reference level is indicative of a test compound that has at least some immunostimulatory capacity. Generally, the negative reference compound is used to set background levels of immunostimulation or
20 immunoinhibition observed in the absence of the test compound. If the reference compound is a positive reference compound (i.e., it is immunostimulatory), then it is possible to compare and contrast the induction profile of the test compound to that of the reference compound.

In some instances, separate reference assays individually containing a positive and a negative reference compound are performed alongside the test assay. For example, if the test
25 assay is a screen for an immunostimulatory TLR ligand, then reference assays can be a positive reference assay (in which the reference compound is immunostimulatory), a negative reference assay (in which the reference compounds is immunologically inert or neutral), or both. A test compound is defined as immunostimulatory if it induces a response greater than that of the negative reference compound. The level and profile of the immunostimulatory
30 response can be compared to the level and profile induced by the positive reference compound. It is to be understood that a test compound that induces a level of immunostimulation less than that of the positive reference compound may still be considered immunostimulatory according to the invention. Modifications to these screening assays for a

- 24 -

desired readout will be apparent to those of ordinary skill in the art based on the teachings provided herein.

If the test assay is a screen for an immunoinhibitory TLR ligand, then the assay may generally involve co-incubation of the test compound and a positive reference compound.

5 The control assay may include co-incubation of the negative and positive reference compounds. As used herein, co-incubation embraces simultaneous or consecutive addition of the reference and test compounds. The test compound may be added before or after the positive reference compound. An immunoinhibitory test compound may be identified by a diminution of the immunostimulatory response induced by the positive reference compound
10 when in the presence of the test compound. If the level of the response is less in the presence of the test compound, this indicates that the test compound is capable of interfering with the immunostimulatory effects of the positive reference compound. As an example, simultaneous or consecutive addition of a putative immunoinhibitory test compound can reduce the amount of cytokines or chemokines secreted by cells in response to the positive reference compound
15 alone, indicating an inhibition of the immunostimulatory effects of the positive reference compound.

The reference immunoinhibitory compound can be used at one or more concentrations in conjunction with a selected or constant concentration of reference immunostimulatory compound. Under proper conditions, the immunostimulatory effect of the reference
20 immunostimulatory compound will be less in the presence of the immunoinhibitory substance than in the absence of the immunoinhibitory substance. Furthermore, under proper conditions, the immunostimulatory effect of the reference immunostimulatory compound will decrease with increasing concentration of the immunoinhibitory substance.

The breadth of response by the cell line to immunomodulatory compounds, and its
25 facile manipulation, allows for the identification of novel compounds. The cell line allows the rapid discovery of such compounds given that it lends itself to high throughput screening methods such as those provided herein. These methods and compositions are described in greater detail below. The invention therefore provides screening methods that utilize cell lines that either endogenous express TLRs such as the RPMI 8226 cell line as well as cell
30 lines that have been modified to express TLRs. The invention further provides compositions that comprise such cell lines.

The verification and standardization methods of the invention generally involve assays in which an isolated cell expressing a functional TLR is contacted with each of two

- 25 -

compositions, each composition containing a known ligand for the TLR. One composition is a reference composition, and the assay using the reference composition yields a reference activity. The second composition is a test composition, and the assay using the test composition yields a test activity. The two contacting steps can be performed on separate cells that are alike, and typically will be performed on separate populations of cells that are alike. For example, the separate cells or the separate populations of cells can be drawn from a single population of cells. In typical usage according to this embodiment, the reference and test activities are measured essentially concurrently, although the use of historical reference activity is also contemplated by the methods of the invention. As an alternative, the two contacting steps can be performed on a single cell or on a single population of cells, usually in an essentially concurrent manner when it is desirable to have competition between reference and test compositions. In one embodiment the known TLR ligand is a nucleic acid molecule.

The assays of the invention are performed under specific conditions so that comparison can be made between reference and test activities or levels. The results of the comparison can be used as a basis upon which to accept or reject the test material as suitable for its intended use.

The biological characterization of the reference composition will generally entail a series of biological activity measurements of the reference composition using a single assay under defined conditions in order to define a range of inter-test variance. The range of inter-test variance so obtained using reference composition can be used to define an acceptable range of variance within which a subsequent test measurement must fall in order to satisfy quality standards. Such a range of acceptable variance can serve as a basis for developing predetermined range of variance about the reference activity, i.e., acceptance criteria for a particular test composition or test lot. For example, a particular reference composition can be assayed under defined conditions in a number of independent measurements and found to yield a result expressed as 100 ± 5 units of activity. Under this same example, a subsequent test measurement of a test composition performed using the same assay and defined conditions is found to yield 97 units of activity. The activity of the test composition under this example thus yielded a result that falls within the normal range of inter-test variance observed for the reference composition. Accordingly, the test material under this example could be selected on the basis of the test activity falling within a predetermined range of variance about the reference activity. In short, the test material can be deemed acceptable

- 26 -

provided the test activity falls within a predetermined range of activity that is related to the activity of the reference material.

In one embodiment, the methods of the invention provide for comparison between a reference lot of a particular TLR ligand and a test lot of the same particular TLR ligand. Such
5 comparison is useful for quality control assessment of the test lot of material, also referred to herein as validation, e.g., product validation. Such comparison is also useful for process validation.

In another embodiment, the methods of the invention provide for comparison between a reference lot of a particular TLR ligand and a test lot of a different TLR ligand. In a simple
10 example, where a test TLR ligand (T) is expected to have little or no activity characteristic of reference TLR ligand (R), comparison can be made between T and R to confirm the lack of R-like activity possessed by T. In a more complex example, where a test TLR ligand (C) is capable of exerting two different effects, wherein each effect is characteristic of one of two different classes of TLR ligand and is best characterized by one of two different reference
15 TLR ligands (A and B), the test TLR ligand (C) can be compared with either of the two reference TLR ligands (A or B). In this second example, test composition C could be found, for example, to possess 50 percent A-like activity compared with reference A and 70 percent B-like activity compared with reference B. Test composition C could thus independently meet or fail to meet predetermined standards for each of A-like activity and B-like activity.
20 Such comparison is also useful for quality control assessment of the test lot of material, e.g., product validation. Of course test TLR ligand C can alternatively or additionally be compared against reference TLR ligand C, as described in the preceding paragraph.

To facilitate the methods of the invention, certain conditions for carrying out the assays are standardized and used for measurements of both reference activity and test activity.
25 In this way direct comparison between reference activity and test activity can be made readily. Conditions that can be standardized and used in this manner can include, without limitation, readout, temperature, media characteristics, duration (time between introduction of reference composition or test composition and activity measurement), methods of sampling, etc. In some embodiments the methods of the invention can be at least partially automated in order to
30 increase throughput and/or to reduce inter-test variability. For example, robotic devices and workstations with the capacity to dispense and/or sample fluids in a set or programmable fashion are now well known in the art and can be used in performing the methods of the instant invention.

- 27 -

In one embodiment a standard curve of reference composition activity is employed. Typically the standard curve is generated by selecting conditions including concentration of the reference composition such that the dose-response curve is essentially linear (and the slope is non-zero) over a range of concentrations that includes the effective concentration at which activity is 50 percent of maximum (EC50). In one embodiment the standard curve spans a range of concentrations defined by $EC50 \pm 1 \log$ concentration, e.g., $1 \times 10^{-7} \text{ M} - 1 \times 10^{-5} \text{ M}$, where EC50 is $1 \times 10^{-6} \text{ M}$. In another embodiment the standard curve spans a broader range of concentrations defined by $EC50 \pm 2 \log$ concentration, e.g., $1 \times 10^{-8} \text{ M} - 1 \times 10^{-4} \text{ M}$, where EC50 is $1 \times 10^{-6} \text{ M}$. In yet another embodiment the standard curve spans a narrower range of concentrations defined by $EC50 \pm 0.5 \log$ concentration, e.g., $3.16 \times 10^{-7} \text{ M} - 3.16 \times 10^{-6} \text{ M}$, where EC50 is $1 \times 10^{-6} \text{ M}$. The foregoing embodiments are intended to be exemplary and not limiting in any way. One of skill in the art will be able to select, for a given reference composition and without undue experimentation, an appropriate range of concentrations about some middle value in order to generate an essentially linear standard curve with a non-zero slope.

In one embodiment a non-linear standard curve of reference and test composition activity is employed. The standard curve can be generated by selecting conditions including concentrations of the reference composition such that the dose-response curve is sigmoidal and the EC50 value can be determined. Comparison of reference and test activity can be done by comparing, e.g., the EC50 values of both curves. Concentration range is chosen to yield a complete sigmoidal response, e.g., concentration should include $EC50 \pm 3 \log$ concentration or $EC50 \pm 4 \log$ concentration. In the case of testing an inhibitory compound the value determined would be the IC50, i.e., concentration where inhibition of the stimulatory signal is half-maximal.

The methods of the invention can be adapted to be automated or at least partially automated methods, as well as to parallel array or high throughput format methods. For example, the assays can be set up using multiwell plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate. Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are

- 28 -

known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the throughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are known in the art for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

Cell lines

The screening methods may use experimental cells. As used herein, an experimental cell is a non-primary cell (i.e., it is not a cell that has been recently harvested from a subject). It excludes, for example, freshly harvested PBMCs. An experimental cell includes a cell from a cell line such as the RPMI 8226 cell line.

In certain embodiments, the cell naturally expresses a functional TLR. In one embodiment relating to the verification and standardization aspects of the invention, the cell may be a PBMC, preferably a PBMC freshly harvested from a subject.

Cells that would be suitable for identification of TLR agonists, antagonists or enhancers according to the invention may possess one or more particular attributes. These attributes include but are not limited to being of human origin, being an immortalized stable cell line, endogenously expressing at least one functional TLR or a combination of functional TLRs, having intact signaling mechanisms, having intact uptake mechanisms, being able to upregulate cytokines, chemokines or cell surface markers, deriving from normal human B cells or from myeloma or B cell leukemia, deriving from human plasmacytoid and myeloid dendritic cells, and readily activatable by TLR ligands such as TLR7 ligands, TLR8 ligands or TLR9 ligands such as CpG nucleic acids or nucleic acids having other immunostimulatory sequence motifs or small molecules such as imidazoquinoline compounds.

In some embodiments, the cell line is the Raji cell line which expresses TLR3, TLR7 and TLR9. This latter cell line secretes, for example, IL-6 and IFN- α 2 upon CpG nucleic acid exposure. In other embodiments, the cell line is RPMI 8226 which expresses TLR7 and TLR9. Upon CpG nucleic acid exposure, this cell line expresses, produces and/or secretes IL-8, IL-10, IP-10 and TNF- α . It also expresses at its cell surface CD86, HLA-DR and CD71. In yet other embodiments, the cell line is the RAMOS cell line which expresses TLR3, TLR7 and TLR9. This cell line at least induces CD80 cell surface expression in response to CpG nucleic acid exposure.

- 29 -

The cell lines have been observed to respond in a concentration dependent manner to TLR ligands such as but not limited to CpG nucleic acids and some non-CpG nucleic acids including T-rich nucleic acids, poly-T nucleic acids and poly-G nucleic acids. The highest responses have been observed using CpG nucleic acids.

5 The screening methods employ a variety of cell lines as shown in the Examples. These include A549 (human lung carcinoma, ATCC CCL-185), BeWo (human choriocarcinoma, ATCC CCL-98), HeLa (human cervix carcinoma, ATCC CCL-2), Hep-2 (human cervix carcinoma, ATCC CCL-23), KG-1 (human acute myeloid leukemia, ATCC CCL-246), MUTZ-3 (human acute myelomonocytic leukemia, German Collection of Cell
10 lines and Microorganisms (DSZM) ACC-295), Nalm-6 (human B cell precursor leukemia, DSZM ACC-128), NK-92 (human Natural killer cell line, ATCC CRL-2407), NK-92 MI (IL-2 independent human Natural killer cell line, ATCC CRL-2408), Raji (human B lymphocyte Burkitt's lymphoma, ATCC CCL-86), RAMOS (B lymphocyte Burkitt's lymphoma, ATCC CRL-1596), RPMI 8226 (human B lymphocyte multiple myeloma, ATCC CCL-155), THP-1
15 (human acute monocytic leukemia, ATCC TIB 202), U937 (human lymphoma, ATCC CRL-1593.2) and Jurkat (human T cell leukemia, ATCC TIB 152).

As shown in the Examples, each of the afore-mentioned cell lines has a particular endogenous TLR expression profile which dictates its suitability in a particular screening assay.

20 A cell that artificially expresses a functional TLR can be a cell that does not express the functional TLR but for a transfected TLR expression vector. For example, human 293 fibroblasts (ATCC CRL-1573) do not express TLR7, TLR8 or TLR9, and they express very little TLR3. As described in the examples below, such cells can be transiently or stably transfected with suitable expression vector (or vectors) so as to yield cells that do express
25 TLR3, TLR7, TLR8, TLR9, or any combination thereof. Alternatively, a cell that artificially expresses a functional TLR can be a cell that expresses the functional TLR at a significantly higher level with the TLR expression vector than it does without the TLR expression vector. Transfected cells are considered modified cells, as used herein.

30 A cell that artificially expresses an expression or reporter construct is preferably stably transfected.

RPMI

- 30 -

The RPMI 8226 cell line is a human multiple myeloma cell line. The cell line was established from the peripheral blood of a 61 year old man at the time of diagnosis for multiple myeloma (IgG lambda type). RPMI 8226 was previously reported as responsive to CpG nucleic acids as evidenced by the production and secretion of IL-6 protein and production of IL-12p40 mRNA. (Takeshita et al. (2000), *Eur. J. Immunol.* 30, 108-116, and Takeshita et al. (2000) *Ibid.* 30, 1967-1976) Takeshita et al. however used the cell line solely to study promoter constructs in order to identify transcription factor binding sites important for CpG nucleic acid signaling. It is now known according to the invention that the cell line produces a number of other chemokines and cytokines including IL-8, IL-10 and IP-10. It has also been discovered according to the invention that the cell line responds to immunostimulatory nucleic acids by upregulating cell surface expression of particular markers. Many of these markers, including CD71, CD86 and HLA-DR, are similarly upregulated in PBMCs exposed to immunostimulatory nucleic acids. This has been observed using flow cytometric analysis of the cell line following CpG nucleic acid exposure. In other aspects of the invention, the cell line can be used in similar screening assays that involve secretion of IL-6, IL-12 and/or TNF- α .

It has recently been discovered that R-848 mediates its immunostimulatory effects via other TLR family members, namely TLR7 and TLR8. TLR7 has previously been found expressed on human B cells. It has now also been discovered according to the invention that RPMI 8226 expresses TLR9 as well as TLR7, thus making it a suitable cell line for identifying immunostimulatory nucleic acid and/or imidazoquinoline (e.g., R-848) mimics or other small molecules that also signal through TLR7 and/or TLR9. Incubation of RPMI 8226 cells with the imidazoquinoline R-848 (Resiquimod) induces for example IL-8, IL-10 and IP-10 production.

Known TLR Ligands

Ligands for many but not all of the TLRs have been described. For instance, it has been reported that TLR1 and TLR2 signals in response to peptidoglycan and lipopeptides. Yoshimura A et al. (1999) *J Immunol* 163:1-5; Brightbill HD et al. (1999) *Science* 285:732-6; Aliprantis AO et al. (1999) *Science* 285:736-9; Takeuchi O et al. (1999) *Immunity* 11:443-51; Underhill DM et al. (1999) *Nature* 401:811-5. TLR4 has been reported to signal in response to lipopolysaccharide (LPS). Hoshino K et al. (1999) *J Immunol* 162:3749-52; Poltorak A et al. (1998) *Science* 282:2085-8; Medzhitov R et al. (1997) *Nature* 388:394-7. Bacterial

flagellin has been reported to be a natural ligand for TLR5. Hayashi F et al. (2001) *Nature* 410:1099-1103. TLR6, in conjunction with TLR2, has been reported to signal in response to proteoglycan. Ozinsky A et al. (2000) *Proc Natl Acad Sci USA* 97:13766-71; Takeuchi O et al. (2001) *Int Immunol* 13:933-40.

- 5 TLR9 is a receptor for CpG DNA. Hemmi H et al. (2000) *Nature* 408:740-5. Other TLR9 ligands are described herein under "Immunostimulatory Nucleic Acids". Certain imidazoquinoline compounds having antiviral activity are ligands of TLR7 and TLR8. Imidazoquinolines are potent synthetic activators of immune cells with antiviral and antitumor properties. R-848 is a ligand for human TLR7 and TLR8. Jurk M et al. (2002) *Nat Immunol* 3:499. Ligands of TLR3 include poly(I:C) and double-stranded RNA (dsRNA). Alexopoulou et al. (2001) *Nature* 413:732-738. For purposes of this invention, poly(I:C) and double-stranded RNA (dsRNA) are classified as oligonucleotide molecules. TLR3 may have a role in host defense against viruses.

15 Reference and Test Compounds

- A test and/or reference compound can be a nucleic acid such as an oligonucleotide or a polynucleotide, an oligopeptide, a polypeptide, a lipid such as a lipopolysaccharide, a carbohydrate such as an oligosaccharide or a polysaccharide, or a small molecule. Alternatively, these compounds may also comprise or be synthesized from elements such as amino acids, carbohydrates, hormones, lipids, organic molecules, and the like.

Small molecules in general include naturally occurring, synthetic, and semisynthetic organic and organometallic compounds with molecular weight less than about 2.5 kDa. Examples of small molecules include most drugs, subunits of polymeric materials, and analogs and derivatives thereof.

- 25 Some specific examples of small molecules include the imidazoquinolines. As used herein, an imidazoquinoline includes imidazoquinoline amines (imidazoquinolinamines), imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2 bridged imidazoquinoline amines. These compounds have been described in U.S. Pat. Nos. 4,689,338; 4,929,624; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,395,937; 5,482,936; 5,494,916; 5,525,612; 6,039,969 and 6,110,929. Particular species of imidazoquinoline agents include resiquimod (R-848; S-28463; 4-amino-2-ethoxymethyl- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol); and imiquimod (R-837; S-26308; 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-4-amine). Further examples of specific small

molecules include 4-aminoquinoline and derivatives thereof, 9-aminoacridine and derivatives thereof, and additional compounds disclosed in U.S. Pat. Nos. 6,221,882; 6,399,630; 6,479,504; and 6,521,637; and published U.S. Pat. Application No. 2002/0151564 A1, the entire contents of which are hereby incorporated by reference.

5 The test and reference compounds may be formulated for pharmaceutical use or not. For example, a test compound not formulated for pharmaceutical use can be a compound (e.g., a lot or batch of the compound) under evaluation for possible use in preparing a pharmaceutical formulation of the compound.

 A reference compound, as used herein, is a compound having a known activity in the
10 presence of a TLR. The reference compound may stimulate TLR signaling (and is therefore regarded as a positive reference compound), or it may be inert in the presence of a TLR (and is therefore regarded as a negative reference compound). If it is a positive reference compound, it need not be the best known stimulator of TLR signaling (i.e., it is possible that other reference compounds and even test compounds will stimulate TLR signaling to a greater
15 extent). The readout of the screening assay may simply be stated relative to the level of signaling that occurs in the presence of the reference compound. Preferably, the reference compound is analyzed prior to the screening assay in order to determine its level of activity on a TLR. In some aspects of the invention, the reference compound and the test compound will be assayed separately (i.e., in separate wells); in other aspects, the reference compound and
20 the test compound will be assayed together (i.e., in the same well). These latter aspects are designed to measure the ability of a test compound to modulate the activity of the reference compound. The activity of the test compound and the reference compound combined (i.e., when assayed together in the same well) may be the same as that of the positive reference compound alone, indicating at a minimum that the test compound is not inhibitory; or it may
25 be less than that of the positive reference compound, indicating at a minimum that it is inhibitory to the effect of the reference compound; or it may be additive or synergistic possibly indicating that the test compound is an enhancer. The effect of an enhance may be due to its ability to stimulate TLR signaling independently of the positive reference compound.

30 A "reference composition" as used herein refers to a composition that includes a reference compound and optionally another agent, e.g., a pharmaceutically acceptable carrier and/or another biologically active agent. A reference compound may be an immunostimulatory compound or it may be an immunoinhibitory compound.

- 33 -

As discussed further below, in some aspects of the invention the reference compositions include both finished products, e.g., finished pharmaceutical products, as well as raw materials and other in-process materials used for the preparation of such finished products, all of which contain a known TLR ligand. As used herein, a "production lot" shall refer to a batch or lot of a completed product prepared for release as clinical material, e.g., a pharmaceutical product. As used herein, an "in-process lot" shall refer to a batch or lot of unfinished product that is prepared in the course of making a production lot; an "in-process lot" shall also refer to a batch or lot of raw material provided for use in the production of a production lot.

In some aspects of the invention, the reference compositions of the invention are highly characterized in terms of their chemical, physical, and biological properties. A reference composition will be a specific composition previously determined to have a specific activity, or range of specific activity, of the particular known TLR ligand present in the composition. As used herein, "specific activity" refers to an amount of activity per unit mass or per unit volume of the reference composition as a whole, as determined using a defined assay under defined conditions. In one embodiment the reference composition is a representative sample of a particular lot or batch of a specific TLR ligand. In one embodiment the reference composition is a representative sample of a particular lot or batch of a specific TLR ligand formulated for pharmaceutical use, e.g., a sterile solution of the TLR ligand at a determined concentration or activity.

At least the following parameters are typically very well defined for a given reference composition: chemical formula of the active ingredient TLR ligand (e.g., nucleobase sequence and type of backbone of a nucleic acid; structural formula of a small molecule); concentration; diluent composition; and purity. Such parameters as purity and concentration can be determined using any appropriate physicochemical method, e.g., optical spectroscopy including absorbance at one or more specified wavelengths; nuclear magnetic resonance (NMR) spectroscopy; mass spectrometry (MS), including matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS); melting point; specific gravity; chromatography including as appropriate high pressure liquid chromatography (HPLC), one- and two-dimensional polyacrylamide gel electrophoresis (PAGE), capillary electrophoresis, and the like; as well as other methods known to those of skill in the art.

Reference compositions can also be very well characterized in terms of their biological activity, independent of the methods of the invention, although the methods of the

- 34 -

invention generally include such characterization, at least in part. A reference composition can be very well characterized in terms of its biological activity by characterizing, both qualitatively and quantitatively, the response by sensitive cells to the reference composition under defined conditions. For example, a reference composition can be a specific CpG oligonucleotide such as SEQ ID NO:1 which in a specific assay and under specific conditions of temperature, concentration, duration of contact between the CpG oligonucleotide and a population of TLR9-expressing cells, and particular readout, reliably yields a specific result or range of results. Results can be expressed in any suitable manner, but can include results expressed on a per-cell basis, e.g., picograms of particular cytokine per cell per hour of contact with the reference composition. Reference compositions can be very well characterized in terms of their biological activity according to one or more parameters, for example, according to their capacity to induce each of a plurality of cytokines.

The methods of the invention also involve measurement of a test activity of a test composition containing a known TLR ligand. A "test composition" as used herein refers to a composition that includes a test compound and optionally another agent, e.g., a pharmaceutically acceptable carrier and/or another biologically active agent. A test compound can be an immunostimulatory compound or it can be an immunoinhibitory compound. In some aspects of the invention, the test compound is a known TLR ligand. Test compositions of the invention may comprise known TLR agonist or TLR antagonist compounds, generally but not necessarily nominally the same as the reference compositions against which comparison is to be made according to some aspects of the invention. Thus test compositions may encompass immunostimulatory compounds, immunoinhibitory compounds, known TLR ligands, finished pharmaceutical products, and raw materials and other in-process materials used for the preparation of such finished products.

Unlike a reference composition, a test composition is not characterized at all, or is only partially characterized, or is not as well characterized as the reference composition, in terms of its chemical, physical, or (most particularly) biological properties. The methods of the invention permit further characterization of the test composition by comparison with a reference composition. In some aspects, a test composition will be a specific composition previously determined to be a ligand of a specific TLR. In one embodiment the test composition is a representative sample of a particular lot or batch of a specific TLR ligand. In one embodiment the test composition is a representative sample of a particular lot or batch of

- 35 -

a specific TLR ligand formulated for pharmaceutical use, e.g., a sterile solution of the TLR ligand at a determined concentration or activity.

Immunostimulatory and Immunoinhibitory Nucleic Acids

5 Nucleic acids useful as reference compounds and as test compounds in the methods of the invention include single- and double-stranded natural and synthetic nucleic acids, including those with phosphodiester, stabilized, and chimeric backbones. Also encompassed are at least the following classes of nucleic acids, which are described in detail below: immunostimulatory CpG nucleic acids (CpG nucleic acids), including but not limited to types
10 A, B, and C; immunostimulatory non-CpG nucleic acids, including without limitation methylated CpG nucleic acids, T-rich nucleic acids, TG-motif nucleic acids, CpI motif nucleic acids, and poly-G nucleic acids; and immunoinhibitory nucleic acids. Nucleic acids useful as reference compounds and as test compounds in the methods of the invention also include nucleic acids with modified backbones, including "soft" and "semi-soft" oligonucleotides as
15 described herein. As will be appreciated from the descriptions below, certain of these various classes of nucleic acids can coexist in a given nucleic acid molecule.

A "nucleic acid" as used herein with respect to test compounds and reference compounds used in the methods of the invention, shall refer to any polymer of two or more individual nucleoside or nucleotide units. Typically individual nucleoside or nucleotide units
20 will include any one or combination of deoxyribonucleosides, ribonucleosides, deoxyribonucleotides, and ribonucleotides. The individual nucleotide or nucleoside units of the nucleic acid can be naturally occurring or not naturally occurring. For example, the individual nucleotide units can include deoxyadenosine, deoxycytidine, deoxyguanosine, thymidine, and uracil. In addition to naturally occurring 2'-deoxy and 2'-hydroxyl forms,
25 individual nucleosides also include synthetic nucleosides having modified base moieties and/or modified sugar moieties, e.g., as described in Uhlmann E et al. (1990) *Chem Rev* 90:543-84. The linkages between individual nucleotide or nucleoside units can be naturally occurring or not naturally occurring. For example, the linkages can be phosphodiester, phosphorothioate, phosphorodithioate, phosphoramidate, as well as peptide linkages and other
30 covalent linkages, known in the art, suitable for joining adjacent nucleoside or nucleotide units. The linkages can also be mixed in a single polymer (e.g., a semi-soft backbone). The nucleic acid test compounds and nucleic acid reference compounds typically range in size from 3-4 units to a few tens of units, e.g., 18-40 units.

In some embodiments the nucleic acids are oligonucleotides made up of 2 to about 100 nucleotides, and more typically 4 to about 40 nucleotides. Oligonucleotides composed exclusively of deoxynucleotides are termed oligodeoxyribonucleotides or, equivalently, oligodeoxynucleotides (ODN).

5 A CpG nucleic acid is an immunostimulatory nucleic acid which contains a cytosine-guanine (CG) dinucleotide, the C residue of which is unmethylated. The effects of CpG nucleic acids on immune modulation have been described extensively in U.S. Pat. Nos. 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; and 6,339,068; and published patent applications, such as PCT/US95/01570 (WO 96/02555); PCT/US98/04703 (WO 98/40100);
10 and PCT/US99/09863 (WO 99/56755). The entire contents of each of these patents and published patent applications is hereby incorporated by reference. The entire immunostimulatory nucleic acid can be unmethylated or portions can be unmethylated, but at least the C of the 5'-CG-3' must be unmethylated. The CpG nucleic acid sequences of the invention include, without limitation, those broadly described above as well as those disclosed
15 in U.S. Pat. Nos. 6,207,646 and 6,239,116.

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:1).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGACGTTTTGTCGTT-3' (SEQ ID NO:139).

20 In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGTCGTTTTTTTCGA-3' (SEQ ID NO:140).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTCGTCGTTTCGTCGTT-3' (SEQ ID NO:141).

25 In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTCGTCGTTTTGTCGTT-3' (SEQ ID NO:142).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTTCGGTCGTTTT-3' (SEQ ID NO:143).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTTCGTGCGTTTTT-3' (SEQ ID NO:144).

30 In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTCGGCGGCCCGCCG-3' (SEQ ID NO:145).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3' (SEQ ID NO:146).

The oligonucleotides described by SEQ ID NOs: 1, 139-145 are fully stabilized phosphorothioate backbone ODN. The oligonucleotide of SEQ ID NO:146 has a chimeric backbone in which all internucleoside linkages are phosphorothioate except for those indicated by “_”, which are phosphodiester.

5 CpG nucleic acids have been further classified by structure and function into at least the following three types, all of which are intended to be encompassed within the methods of the instant invention: Type B CpG nucleic acids such as SEQ ID NO:1 include the earliest described CpG nucleic acids and characteristically activate B cells but do not induce or only weakly induce expression of IFN- α . Type B nucleic acids are described in U.S. Patents
10 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; and 6,339,068. Type A CpG nucleic acids, described in published international application PCT/US00/26527 (WO 01/22990), incorporate a CpG motif, include a hybrid phosphodiester/phosphorothioate backbone, and characteristically induce plasmacytoid dendritic cells to express large amounts of IFN- α but do not activate or only weakly activate B cells. Type C oligonucleotides incorporate a CpG,
15 include a chimeric backbone, include a GC-rich palindromic or nearly-palindromic region, and are capable of both activating B cells and inducing expression of IFN- α . These have been described, for example, in copending U.S. Pat. application Ser. No. 10/224,523, filed August 19, 2002. Exemplary sequences of A, B and C class nucleic acids are described in the afore-mentioned references, patents and patent applications, the entire contents of which are
20 hereby incorporated by reference herein.

In other embodiments of the invention, a non-CpG nucleic acid is used. A non-CpG nucleic acid is an immunostimulatory nucleic acid which either does not have a CpG motif in its sequence, or has a CpG motif which contains a methylated C residue. In some instances, the non-CpG nucleic acid may still be immunostimulatory by virtue of its having other
25 immunostimulatory motifs such as those described herein and known in the art. In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid. In some instances the non-CpG nucleic acid is still immunostimulatory despite methylation of the C of the CpG motif, even without having another non-CpG immunostimulatory motif described herein and known in the art.

30 In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-TZGTZGTTTTGTZGTTTTGTZGTT-3' (SEQ ID NO:147), wherein Z represents 5-methylcytosine.

- 38 -

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-TZGTZGZTGTZTZZGZTTZTTZTTGZZ-3' (SEQ ID NO:148), wherein Z represents 5-methylcytosine.

5 In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-GZGTTTGZTZZTTZTTZTTGZG-3' (SEQ ID NO:149), wherein Z represents 5-methylcytosine.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-GZZZAAGZTGGZATZZGTZA-3' (SEQ ID NO:150), wherein Z represents 5-methylcytosine.

10 Non-CpG nucleic acids include T-rich immunostimulatory nucleic acids. The T-rich immunostimulatory nucleic acids include those disclosed in published PCT patent application PCT/US00/26383 (WO 01/22972), the entire contents of which are incorporated herein by reference. In some embodiments, T-rich nucleic acids 24 bases in length are used. A T-rich nucleic acid is a nucleic acid which includes at least one poly T sequence and/or which has a
15 nucleotide composition of greater than 25% T nucleotide residues. A nucleic acid having a poly-T sequence includes at least four Ts in a row, such as 5'-TTTT-3'. In some embodiments the T-rich nucleic acid includes more than one poly T sequence. In important embodiments, the T-rich nucleic acid may have 2, 3, 4, or more poly T sequences, such as SEQ ID NO:1.

Non-CpG nucleic acids also include poly-G immunostimulatory nucleic acids. A
20 variety of references describe the immunostimulatory properties of poly-G nucleic acids. Pisetsky DS et al. (1993) *Mol Biol Reports* 18:217-221; Krieger M et al. (1994) *Ann Rev Biochem* 63:601-637; Macaya RF et al. (1993) *Proc Natl Acad Sci USA* 90:3745-3749; Wyatt JR et al. (1994) *Proc Natl Acad Sci USA* 91:1356-1360; Rando and Hogan, 1998, In *Applied Antisense Oligonucleotide Technology*, Krieg and Stein, eds., pp. 335-352; Kimura Y et al.
25 (1994) *J Biochem (Tokyo)* 116:991-994.

The immunostimulatory nucleic acids of the invention can also be those which do not possess CpG, methylated CpG, T-rich, or poly-G motifs.

Exemplary immunostimulatory nucleic acid sequences include but are not limited to those immunostimulatory sequences described and listed in U.S. Non-Provisional Pat.
30 Application No. 09/669,187, filed on September 25, 2000, and in corresponding published PCT patent application PCT/US00/26383 (WO 01/22972).

Immunoinhibitory nucleic acids have been described in Lenert P et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:247-56 and in Stunz L et al. (2002) *Eur J Immunol*

32:1212-22. These inhibitory phosphorothioate ODN (S-ODN) differ from stimulatory S-ODN by having 2-3 G substitutions in the central motif. As inhibitory S-ODN did not directly interfere with the NF- κ B DNA binding but prevented CpG-induced NF- κ B nuclear translocation of p50, p65, and c-Rel and blocked p105, I κ B α , and I κ B β degradation, Lenert et al. suggested that the putative target of immunoinhibitory ODN would lie upstream of inhibitory kinase (IKK) activation. Stunz et al. reported that replacing GCGTT or ACGTT with GCGGG or ACGGG converted a stimulatory 15-mer ODN into an inhibitory ODN. All inhibitory ODN had three consecutive G, and a fourth G increased inhibitory activity, but a deazaguanosine substitution to prevent planar stacking did not affect activity. Inhibitory ODN blocked apoptosis protection and cell-cycle entry induced by stimulatory ODN, but not that induced by lipopolysaccharide, anti-CD40 or anti-IgM+IL-4. ODN-driven up-regulation of cyclin D(2), c-Myc, c-Fos, c-Jun and Bcl(XL) and down-regulation of cyclin kinase inhibitor p27(kip1) were all blocked by inhibitory ODN. Stunz et al. also reported that interference with uptake of stimulatory ODN did not account for the inhibitory effects of the immunoinhibitory nucleic acids.

In one embodiment the immunoinhibitory nucleic acid has a base sequence provided by 5'-TCCTGGCGGGGAAGT-3' (SEQ ID NO:151).

Immunoinhibitory nucleic acids have also been described in U.S. Pat. No. 6,194,388, issued to Krieg et al. The immunoinhibitory oligonucleotides disclosed by Krieg et al. are oligonucleotides with GCG trinucleotides at or near the ends of the oligonucleotide and are represented by the formula 5' GCGX_nGCG 3' in which X is a nucleotide and n is an integer between 0 and 50.

The nucleic acids used as either test or reference compounds can be double-stranded or single-stranded. They can be deoxyribonucleotide (DNA) or ribonucleotide (RNA) molecules. Generally, double-stranded molecules are more stable in vivo, while single-stranded molecules have increased immune activity. Thus in some the nucleic acid is single-stranded and in other embodiments the nucleic acid is double-stranded. In certain embodiments, while the nucleic acid is single-stranded, it is capable of forming secondary and tertiary structures (e.g., by folding back on itself, or by hybridizing with itself either throughout its entirety or at select segments along its length). Accordingly, while the primary structure of such a nucleic acid may be single-stranded, its higher order structures may be double- or triple-stranded.

For facilitating uptake into cells, the nucleic acids are preferably in the range of 6 to 100 bases in length. However, nucleic acids of any size equal to or greater than 6 nucleotides (even many kb long) are capable of inducing an immune response. Preferably the nucleic acid is in the range of between 8 and 100 and in some embodiments between 8 and 50 or 8 and 30 nucleotides in size.

The terms "nucleic acid" and "oligonucleotide" are used interchangeably to mean multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)). As used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms "nucleic acid" and "oligonucleotide" shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base containing polymer. Nucleic acid molecules can be obtained from existing nucleic acid sources (e.g., genomic or cDNA), but are preferably synthetic (e.g., produced by nucleic acid synthesis).

The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with substitutions or modifications, such as in the bases and/or sugars. For example, they include nucleic acids having backbone sugars that are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group or hydroxy group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose or 2'-fluoroarabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have an amino acid backbone with nucleic acid bases). Other examples are described in more detail below.

The immunostimulatory and immunoinhibitory nucleic acids can encompass various chemical modifications and substitutions, in comparison to natural RNA and DNA, involving a phosphodiester internucleoside bridge, a β -D-ribose unit and/or a natural nucleoside base (adenine, guanine, cytosine, thymine, uracil). Examples of chemical modifications are known to the skilled person and are described, for example, in Uhlmann E et al. (1990) *Chem Rev* 90:543; "Protocols for Oligonucleotides and Analogs" Synthesis and Properties & Synthesis and Analytical Techniques, S. Agrawal, Ed, Humana Press, Totowa, USA 1993; Crooke ST et al. (1996) *Annu Rev Pharmacol Toxicol* 36:107-129; and Hunziker J et al. (1995) *Mod Synth*

Methods 7:331-417. An oligonucleotide according to the invention may have one or more modifications, wherein each modification is located at a particular phosphodiester internucleoside bridge and/or at a particular β -D-ribose unit and/or at a particular natural nucleoside base position in comparison to an oligonucleotide of the same sequence which is composed of natural DNA or RNA.

For example, the oligonucleotides may comprise one or more modifications and wherein each modification is independently selected from:

- a) the replacement of a phosphodiester internucleoside bridge located at the 3' and/or the 5' end of a nucleoside by a modified internucleoside bridge,
- 10 b) the replacement of phosphodiester bridge located at the 3' and/or the 5' end of a nucleoside by a dephospho bridge,
- c) the replacement of a sugar phosphate unit from the sugar phosphate backbone by another unit,
- d) the replacement of a β -D-ribose unit by a modified sugar unit, and
- 15 e) the replacement of a natural nucleoside base by a modified nucleoside base.

More detailed examples for the chemical modification of an oligonucleotide are as follows.

The oligonucleotides may include modified internucleotide linkages, such as those described in (a) or (b) above. These modified linkages may be partially resistant to degradation (e.g., are stabilized). A "stabilized oligonucleotide molecule" shall mean an oligonucleotide that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endonuclease) resulting from such modifications. Oligonucleotides having phosphorothioate linkages, in some embodiments, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases.

25 A phosphodiester internucleoside bridge located at the 3' and/or the 5' end of a nucleoside can be replaced by a modified internucleoside bridge, wherein the modified internucleoside bridge is for example selected from phosphorothioate, phosphorodithioate, NR^1R^2 -phosphoramidate, boranophosphate, α -hydroxybenzyl phosphonate, phosphate-(C_1 - C_{21})-O-alkyl ester, phosphate-[(C_6 - C_{12})aryl-(C_1 - C_{21})-O-alkyl]ester, (C_1 - C_8)alkylphosphonate and/or (C_6 - C_{12})arylphosphonate bridges, (C_7 - C_{12})- α -hydroxymethyl-aryl (e.g., disclosed in WO 95/01363), wherein (C_6 - C_{12})aryl, (C_6 - C_{20})aryl and (C_6 - C_{14})aryl are optionally substituted by halogen, alkyl, alkoxy, nitro, cyano, and where R^1 and R^2 are, independently of each other, hydrogen, (C_1 - C_{18})-alkyl, (C_6 - C_{20})-aryl, (C_6 - C_{14})-aryl-(C_1 - C_8)-alkyl, preferably hydrogen,

(C₁-C₈)-alkyl, preferably (C₁-C₄)-alkyl and/or methoxyethyl, or R¹ and R² form, together with the nitrogen atom carrying them, a 5-6-membered heterocyclic ring which can additionally contain a further heteroatom from the group O, S and N.

The replacement of a phosphodiester bridge located at the 3' and/or the 5' end of a nucleoside by a dephospho bridge (dephospho bridges are described, for example, in Uhlmann E and Peyman A in "Methods in Molecular Biology", Vol. 20, "Protocols for Oligonucleotides and Analogs", S. Agrawal, Ed., Humana Press, Totowa, 1993, Chapter 16, pp. 355 ff), wherein a dephospho bridge is for example selected from the dephospho bridges formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethyl-hydrazo, dimethylenesulfone and/or silyl groups.

A sugar phosphate unit (i.e., a β -D-ribose and phosphodiester internucleoside bridge together forming a sugar phosphate unit) from the sugar phosphate backbone (i.e., a sugar phosphate backbone is composed of sugar phosphate units) can be replaced by another unit, wherein the other unit is for example suitable to build up a "morpholino-derivative" oligomer (as described, for example, in Stirchak EP et al. (1989) *Nucleic Acids Res* 17:6129-41), that is, e.g., the replacement by a morpholino-derivative unit; or to build up a polyamide nucleic acid ("PNA"; as described for example, in Nielsen PE et al. (1994) *Bioconjug Chem* 5:3-7), that is, e.g., the replacement by a PNA backbone unit, e.g., by 2-aminoethylglycine. The oligonucleotide may have other carbohydrate backbone modifications and replacements, such as peptide nucleic acids with phosphate groups (PHONA), locked nucleic acids (LNA), and oligonucleotides having backbone sections with alkyl linkers or amino linkers. The alkyl linker may be branched or unbranched, substituted or unsubstituted, and chirally pure or a racemic mixture.

A β -ribose unit or a β -D-2'-deoxyribose unit can be replaced by a modified sugar unit, wherein the modified sugar unit is for example selected from β -D-ribose, α -D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-F-arabinose, 2'-O-(C₁-C₆)alkyl-ribose, preferably 2'-O-(C₁-C₆)alkyl-ribose is 2'-O-methylribose, 2'-O-(C₂-C₆)alkenyl-ribose, 2'-[O-(C₁-C₆)alkyl-O-(C₁-C₆)alkyl]-ribose, 2'-NH₂-2'-deoxyribose, β -D-xylo-furanose, α -arabinofuranose, 2,4-dideoxy- β -D-erythro-hexo-pyranose, and carbocyclic (described, for example, in Froehler J (1992) *Am Chem Soc* 114:8320) and/or open-chain sugar analogs (described, for example, in Vandendriessche et al. (1993) *Tetrahedron* 49:7223) and/or bicyclosugar analogs (described, for example, in Tarkov M et al. (1993) *Helv Chim Acta* 76:481).

In some embodiments the sugar is 2'-O-methylribose, particularly for one or both nucleotides linked by a phosphodiester or phosphodiester-like internucleoside linkage.

In some embodiments, the nucleic acids may be soft or semi-soft nucleic acids. A soft nucleic acid is an immunostimulatory nucleic acid having a partially stabilized backbone, in which phosphodiester or phosphodiester-like internucleotide linkages occur only within and immediately adjacent to at least one internal pyrimidine-purine dinucleotide (YZ). Preferably YZ is YG, a pyrimidine-guanosine (YG) dinucleotide. The at least one internal YZ dinucleotide itself has a phosphodiester or phosphodiester-like internucleotide linkage. A phosphodiester or phosphodiester-like internucleotide linkage occurring immediately adjacent to the at least one internal YZ dinucleotide can be 5', 3', or both 5' and 3' to the at least one internal YZ dinucleotide.

In particular, phosphodiester or phosphodiester-like internucleotide linkages involve "internal dinucleotides". An internal dinucleotide in general shall mean any pair of adjacent nucleotides connected by an internucleotide linkage, in which neither nucleotide in the pair of nucleotides is a terminal nucleotide, i.e., neither nucleotide in the pair of nucleotides is a nucleotide defining the 5' or 3' end of the nucleic acid. Thus a linear nucleic acid that is n nucleotides long has a total of n-1 dinucleotides and only n-3 internal dinucleotides. Each internucleotide linkage in an internal dinucleotide is an internal internucleotide linkage. Thus a linear nucleic acid that is n nucleotides long has a total of n-1 internucleotide linkages and only n-3 internal internucleotide linkages. The strategically placed phosphodiester or phosphodiester-like internucleotide linkages, therefore, refer to phosphodiester or phosphodiester-like internucleotide linkages positioned between any pair of nucleotides in the nucleic acid sequence. In some embodiments the phosphodiester or phosphodiester-like internucleotide linkages are not positioned between either pair of nucleotides closest to the 5' or 3' end.

Preferably a phosphodiester or phosphodiester-like internucleotide linkage occurring immediately adjacent to the at least one internal YZ dinucleotide is itself an internal internucleotide linkage. Thus for a sequence N_1 YZ N_2 , wherein N_1 and N_2 are each, independent of the other, any single nucleotide, the YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, and in addition (a) N_1 and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N_1 is an internal nucleotide, (b) Z and N_2 are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N_2 is an internal nucleotide, or (c) N_1 and Y are linked by a phosphodiester or

- 44 -

phosphodiester-like internucleotide linkage when N_1 is an internal nucleotide and Z and N_2 are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N_2 is an internal nucleotide.

Soft nucleic acids according to the instant invention are believed to be relatively
5 susceptible to nuclease cleavage compared to completely stabilized nucleic acids. Without meaning to be bound to a particular theory or mechanism, it is believed that soft nucleic acids of the invention are cleavable to fragments with reduced or no immunostimulatory activity relative to full-length soft nucleic acids. Incorporation of at least one nuclease-sensitive internucleotide linkage, particularly near the middle of the nucleic acid, is believed to provide
10 an "off switch" which alters the pharmacokinetics of the nucleic acid so as to reduce the duration of maximal immunostimulatory activity of the nucleic acid. This can be of particular value in tissues and in clinical applications in which it is desirable to avoid injury related to chronic local inflammation or immunostimulation, e.g., the kidney.

A semi-soft nucleic acid is an immunostimulatory nucleic acid having a partially
15 stabilized backbone, in which phosphodiester or phosphodiester-like internucleotide linkages occur only within at least one internal pyrimidine-purine (YZ) dinucleotide. Semi-soft nucleic acids generally possess increased immunostimulatory potency relative to corresponding fully stabilized immunostimulatory nucleic acids. Due to the greater potency of semi-soft nucleic acids, semi-soft nucleic acids may be used, in some instances, at lower
20 effective concentrations and have lower effective doses than conventional fully stabilized immunostimulatory nucleic acids in order to achieve a desired biological effect.

It is believed that the foregoing properties of semi-soft nucleic acids generally increase with increasing "dose" of phosphodiester or phosphodiester-like internucleotide linkages involving internal YZ dinucleotides. Thus it is believed, for example, that generally for a
25 given nucleic acid sequence with five internal YZ dinucleotides, a nucleic acid with five internal phosphodiester or phosphodiester-like YZ internucleotide linkages is more immunostimulatory than a nucleic acid with four internal phosphodiester or phosphodiester-like YG internucleotide linkages, which in turn is more immunostimulatory than a nucleic acid with three internal phosphodiester or phosphodiester-like YZ internucleotide linkages,
30 which in turn is more immunostimulatory than a nucleic acid with two internal phosphodiester or phosphodiester-like YZ internucleotide linkages, which in turn is more immunostimulatory than a nucleic acid with one internal phosphodiester or phosphodiester-like YZ internucleotide linkage. Importantly, inclusion of even one internal phosphodiester or

- 45 -

phosphodiester-like YZ internucleotide linkage is believed to be advantageous over no internal phosphodiester or phosphodiester-like YZ internucleotide linkage. In addition to the number of phosphodiester or phosphodiester-like internucleotide linkages, the position along the length of the nucleic acid can also affect potency.

5 The soft and semi-soft nucleic acids will generally include, in addition to the phosphodiester or phosphodiester-like internucleotide linkages at preferred internal positions, 5' and 3' ends that are resistant to degradation. Such degradation-resistant ends can involve any suitable modification that results in an increased resistance against exonuclease digestion over corresponding unmodified ends. For instance, the 5' and 3' ends can be stabilized by the
10 inclusion thereof at least one phosphate modification of the backbone. In a preferred embodiment, the at least one phosphate modification of the backbone at each end is independently a phosphorothioate, phosphorodithioate, methylphosphonate, or methylphosphorothioate internucleotide linkage. In another embodiment, the degradation-resistant end includes one or more nucleotide units connected by peptide or amide linkages at
15 the 3' end.

A phosphodiester internucleotide linkage is the type of linkage characteristic of nucleic acids found in nature. The phosphodiester internucleotide linkage includes a phosphorus atom flanked by two bridging oxygen atoms and bound also by two additional oxygen atoms, one charged and the other uncharged. Phosphodiester internucleotide linkage
20 is particularly preferred when it is important to reduce the tissue half-life of the nucleic acid.

A phosphodiester-like internucleotide linkage is a phosphorus-containing bridging group that is chemically and/or diastereomerically similar to phosphodiester. Measures of similarity to phosphodiester include susceptibility to nuclease digestion and ability to activate RNase H. Thus for example phosphodiester, but not phosphorothioate, nucleic acids are
25 susceptible to nuclease digestion, while both phosphodiester and phosphorothioate nucleic acids activate RNase H. In a preferred embodiment the phosphodiester-like internucleotide linkage is boranophosphate (or equivalently, boranophosphonate) linkage. U.S. Patent No. 5,177,198; U.S. Patent No. 5,859,231; U.S. Patent No. 6,160,109; U.S. Patent No. 6,207,819; Sergueev et al., (1998) *J Am Chem Soc* 120:9417-27. In another preferred embodiment the
30 phosphodiester-like internucleotide linkage is diastereomerically pure Rp phosphorothioate. It is believed that diastereomerically pure Rp phosphorothioate is more susceptible to nuclease digestion and is better at activating RNase H than mixed or diastereomerically pure Sp phosphorothioate. Stereoisomers of CpG nucleic acids are the subject of co-pending U.S.

patent application 09/361,575 filed July 27, 1999, and published PCT application PCT/US99/17100 (WO 00/06588). It is to be noted that for purposes of the instant invention, the term "phosphodiester-like internucleotide linkage" specifically excludes phosphorodithioate and methylphosphonate internucleotide linkages.

- 5 As described above the soft and semi-soft nucleic acids of the invention may have phosphodiester like linkages between C and G. One example of a phosphodiester-like linkage is a phosphorothioate linkage in an R_p conformation. Nucleic acid p-chirality can have apparently opposite effects on the immune activity of a CpG nucleic acid, depending upon the time point at which activity is measured. At an early time point of 40 minutes, the R_p but not
- 10 the S_p stereoisomer of phosphorothioate CpG nucleic acid induces JNK phosphorylation in mouse spleen cells. In contrast, when assayed at a late time point of 44 hr, the S_p but not the R_p stereoisomer is active in stimulating spleen cell proliferation. This difference in the kinetics and bioactivity of the R_p and S_p stereoisomers does not result from any difference in cell uptake, but rather most likely is due to two opposing biologic roles of the p-chirality.
- 15 First, the enhanced activity of the R_p stereoisomer compared to the S_p for stimulating immune cells at early time points indicates that the R_p may be more effective at interacting with the CpG receptor, TLR9, or inducing the downstream signaling pathways. On the other hand, the faster degradation of the R_p PS-nucleic acids compared to the S_p results in a much shorter duration of signaling, so that the S_p PS-nucleic acids appear to be more biologically
- 20 active when tested at later time points.

A surprisingly strong effect is achieved by the p-chirality at the CpG dinucleotide itself. In comparison to a stereo-random CpG nucleic acid the congener in which the single CpG dinucleotide was linked in R_p was slightly more active, while the congener containing an S_p linkage was nearly inactive for inducing spleen cell proliferation.

- 25 Nucleic acids also include substituted purines and pyrimidines such as C-5 propyne pyrimidine and 7-deaza-7-substituted purine modified bases. Wagner RW et al. (1996) *Nat Biotechnol* 14:840-4. Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, and thymine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

- 30 A modified base is any base which is chemically distinct from the naturally occurring bases typically found in DNA and RNA such as T, C, G, A, and U, but which share basic chemical structures with these naturally occurring bases. The modified nucleoside base may be, for example, selected from hypoxanthine, uracil, dihydrouracil, pseudouracil, 2-thiouracil,

- 47 -

4-thiouracil, 5-aminouracil, 5-(C₁-C₆)-alkyluracil, 5-(C₂-C₆)-alkenyluracil, 5-(C₂-C₆)-alkynyluracil, 5-(hydroxymethyl)uracil, 5-chlorouracil, 5-fluorouracil, 5-bromouracil, 5-hydroxycytosine, 5-(C₁-C₆)-alkylcytosine, 5-(C₂-C₆)-alkenylcytosine, 5-(C₂-C₆)-alkynylcytosine, 5-chlorocytosine, 5-fluorocytosine, 5-bromocytosine, N²-dimethylguanine, 2,4-diamino-purine, 8-azapurine, a substituted 7-deazapurine, preferably 7-deaza-7-substituted and/or 7-deaza-8-substituted purine, 5-hydroxymethylcytosine, N4-alkylcytosine, e.g., N4-ethylcytosine, 5-hydroxydeoxycytidine, 5-hydroxymethyldeoxycytidine, N4-alkyldeoxycytidine, e.g., N4-ethyldeoxycytidine, 6-thiodeoxyguanosine, and deoxyribonucleosides of nitropyrrole, C5-propynylpyrimidine, and diaminopurine e.g., 2,6-diaminopurine, inosine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, hypoxanthine or other modifications of a natural nucleoside bases. This list is meant to be exemplary and is not to be interpreted to be limiting.

Modified cytosines include but are not limited to 5-substituted cytosines (e.g., 5-methyl-cytosine, 5-fluoro-cytosine, 5-chloro-cytosine, 5-bromo-cytosine, 5-iodo-cytosine, 5-hydroxy-cytosine, 5-hydroxymethyl-cytosine, 5-difluoromethyl-cytosine, and unsubstituted or substituted 5-alkynyl-cytosine), 6-substituted cytosines, N4-substituted cytosines (e.g., N4-ethyl-cytosine), 5-aza-cytosine, 2-mercapto-cytosine, isocytosine, pseudo-isocytosine, cytosine analogs with condensed ring systems (e.g., N,N'-propylene cytosine or phenoxazine), and uracil and its derivatives (e.g., 5-fluoro-uracil, 5-bromo-uracil, 5-bromovinyl-uracil, 4-thio-uracil, 5-hydroxy-uracil, 5-propynyl-uracil). In another embodiment, the cytosine base is substituted by a universal base (e.g., 3-nitropyrrole, P-base), an aromatic ring system (e.g., fluorobenzene or difluorobenzene) or a hydrogen atom (dSpacer).

Modified guanines include but are not limited to 7-deazaguanine, 7-deaza-7-substituted guanine (such as 7-deaza-7-(C₂-C₆)alkynylguanine), 7-deaza-8-substituted guanine, hypoxanthine, N2-substituted guanines (e.g., N2-methyl-guanine), 5-amino-3-methyl-3H,6H-thiazolo[4,5-d]pyrimidine-2,7-dione, 2,6-diaminopurine, 2-aminopurine, purine, indole, adenine, substituted adenines (e.g., N6-methyl-adenine, 8-oxo-adenine) 8-substituted guanine (e.g., 8-hydroxyguanine and 8-bromoguanine), and 6-thioguanine. In another embodiment, the guanine base is substituted by a universal base (e.g., 4-methyl-indole, 5-nitro-indole, and K-base), an aromatic ring system (e.g., benzimidazole or dichloro-benzimidazole, 1-methyl-1H-[1,2,4]triazole-3-carboxylic acid amide) or a hydrogen atom (dSpacer).

For use in the instant invention, the oligonucleotide reference compounds and test compounds can be synthesized *de novo* using any of a number of procedures well known in the art, for example, the β -cyanoethyl phosphoramidite method (Beaucage SL et al. (1981) *Tetrahedron Lett* 22:1859), or the nucleoside H-phosphonate method (Garegg et al. (1986) *Tetrahedron Lett* 27:4051-4; Froehler BC et al. (1986) *Nucleic Acids Res* 14:5399-407; Garegg et al (1986) *Tetrahedron Lett* 27:4055-8; Gaffney et al. (1988) *Tetrahedron Lett* 29:2619-22). These chemistries can be performed by a variety of automated nucleic acid synthesizers available in the market. These oligonucleotides are referred to as synthetic oligonucleotides. An isolated oligonucleotide generally refers to an oligonucleotide which is separated from components which it is normally associated with in nature. As an example, an isolated oligonucleotide may be one which is separated from a cell, from a nucleus, from mitochondria or from chromatin.

Modified backbones such as phosphorothioates can be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Pat. No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described (e.g., Uhlmann E et al. (1990) *Chem Rev* 90:544; Goodchild J (1990) *Bioconjugate Chem* 1:165).

TLR expression

The cell lines can be used in their native state without any modification. For example, in the case of the RPMI 8226 cell line, it can be used to identify compounds that signal through at least TLR9 and/or TLR7. In other instances, however, the cell line can be modified to express a TLR that it does not naturally express. In still other instances, the cell to be used in the screening method may express one or more endogenous TLR and yet still be manipulated to express an additional TLR different from those it endogenously expresses. The cell may also be manipulated in order to increase or decrease the level of TLR that it endogenously expresses. The cells may be stably or transiently transfected.

A cell that does not naturally express a protein or polypeptide, but is genetically manipulated to do so is referred to as ectopically expressing the protein or polypeptide.

The basic screening method remains the same regardless of which TLR is expressed by the cell. However, the reference compound and the readout may vary depending upon the TLR(s) expressed. In the most simple aspect, the screening method is used to identify a compound that signals through a TLR such as for example TLR9. In this case, the positive
5 reference compound may be an immunostimulatory compound already known to act through TLR9 (e.g., CpG nucleic acid).

The methods of the invention involve, in part, contacting a functional TLR with a test composition. A functional TLR is a full-length TLR protein or a fragment thereof capable of inducing or inhibiting a signal in response to interaction with its ligand. Generally the
10 functional TLR will include at least a TLR ligand-binding fragment of the extracellular domain of the full-length TLR and at least a fragment of a TIR domain capable of interacting with another Toll homology domain-containing polypeptide, e.g., MyD88. In various embodiments the functional TLR is a full-length TLR selected from TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR10.

To date, there are eleven TLRs known. Nucleic acid and amino acid sequences for ten
15 currently known human TLRs are available from public databases such as GenBank. Similarly, nucleic acid and amino acid sequences for various TLRs from numerous non-human species are also available from public databases including GenBank. For example, nucleic acid and amino acid sequences for human TLR9 (hTLR9) can be found as GenBank
20 accession numbers AF245704 (coding region spanning nucleotides 145-3243) (SEQ ID NO: 60) and AAF78037 (SEQ ID NO: 62), respectively. Nucleic acid and amino acid sequences for murine TLR9 (mTLR9) can be found as GenBank accession numbers AF348140 (coding region spanning nucleotides 40-3138) (SEQ ID NO: 68) and AAK29625 (SEQ ID NO: 72), respectively.

Nucleic acid and amino acid sequences for human TLR8 (hTLR8) can be found as
25 GenBank accession numbers AF245703 (coding region spanning nucleotides 49-3174) (SEQ ID NO: 46) and AAF78036 (SEQ ID NO: 50), respectively. Nucleic acid and amino acid sequences for murine TLR8 (mTLR8) can be found as GenBank accession numbers AY035890 (coding region spanning nucleotides 59-3157) (SEQ ID NO: 55) and AAK62677
30 (SEQ ID NO: 57), respectively.

Nucleic acid and amino acid sequences for human TLR7 (hTLR7) can be found as GenBank accession numbers AF240467 (coding region spanning nucleotides 135-3285) (SEQ ID NO: 31) and AAF60188 (SEQ ID NO: 34), respectively. Nucleic acid and amino acid

sequences for murine TLR7 (mTLR7) can be found as GenBank accession numbers AY035889 (coding region spanning nucleotides 49-3201) (SEQ ID NO: 38) and AAK62676 (SEQ ID NO: 41), respectively.

5 Nucleic acid and amino acid sequences for human TLR3 (hTLR3) can be found as GenBank accession numbers NM_003265 (coding region spanning nucleotides 102-2816) (SEQ ID NO: 7) and NP_003256 (SEQ ID NO: 8), respectively. Nucleic acid and amino acid sequences for murine TLR3 (hTLR3) can be found as GenBank accession numbers AF355152 (coding region spanning nucleotides 44-2761) (SEQ ID NO: 9) and AAK26117 (SEQ ID NO: 10), respectively.

10 Nucleic acid and amino acid sequences for human TLR1 (hTLR1) can be found as GenBank accession numbers NM_003263 and NP_003254, respectively. Nucleic acid and amino acid sequences for murine TLR1 (mTLR1) can be found as GenBank accession numbers NM_030682 and NP_109607, respectively.

The functional TLR also is not limited to native TLR polypeptides. As used herein, a native TLR is one that is naturally occurring. The TLR may be a non-native (or non-naturally occurring TLR). An example is a chimeric TLR having an extracellular domain and the cytoplasmic domain derived from TLRs from different species. Such chimeric TLR polypeptides can include, for example, a human TLR extracellular domain and a murine TLR cytoplasmic domain. In alternative embodiments, such chimeric TLR polypeptides can include chimerae created with different TLR splice variants or allotypes.

15
20

TLR Signaling Pathways

The screening methods provided by the invention measure TLR signaling activity. TLR signaling activity is activity that results from interaction of a TLR with a TLR ligand. TLR signaling can be measured in a number of ways including but not limited to interaction between a TLR and a protein or factor (such as an adaptor protein), interaction between downstream proteins or factors (such as an adaptor protein) with each other, activation of nuclear factors such as transcription factors or transcription complexes, up- or down-regulation of genes, phosphorylation or dephosphorylation of proteins or factors in the signaling cascade, expression, production and/or secretion of cytokines and/or chemokines, changes in cell cycle status, up- or down-regulation of cell surface marker expression, and the like. Those of ordinary skill in the art are familiar with assays for measuring these latter

25
30

events including but not limited to gel shift assays, immunoprecipitations, phosphorylation status analysis of proteins, Northern analysis, RT-PCR analysis, etc.

The following is an exemplary TLR signaling pathway or cascade. It is to be understood that this is meant to be illustrative and that different factors may be involved in the signaling of particular TLR. One TLR signaling pathway is known to use the cytoplasmic Toll/IL-1 receptor (TIR) homology domain, present in all TLRs. This domain interacts (e.g., binds to) and thereby transduces a signal to a similar domain on an adapter protein (e.g., MyD88). This type of interaction is referred to as a like:like interaction of TIR domains. This interaction is followed by an another interaction between the adapter protein and a kinase, through their respective "death domains". In the case of at least TLR4 signaling, the kinase then interacts with tumor necrosis factor (TNF) receptor-associated factor-6 (TRAF6). Medzhitov R et al., *Mol Cell* 2:253 (1998); Kopp EB et al., *Curr Opin Immunol* 11:15 (1999). After TRAF6, two sequential kinase activation steps lead to phosphorylation of the inhibitory protein I kappa B and its dissociation from NF- κ B. The first kinase is a mitogen-activated kinase kinase kinase (MAPKKK) known as NIK, for NF- κ B-inducing kinase. The target of this kinase is another kinase made up of two chains, called I kappa B kinase α (IKK α) and I kappa B kinase β (IKK β), that together form a heterodimer of IKK α :IKK β , which phosphorylates I kappa B. NF- κ B translocates to the nucleus to activate genes with kappa B binding sites in their promoters and enhancers such as the genes encoding IL-6, IL-8, the p40 subunit of IL-12, and the costimulatory molecule CD86. The signaling mechanisms of TLRs are not limited to this pathway; other signaling pathways exist and can be used in the screening readouts of the methods provided herein.

The screening assays employ a number of readouts (or parameters). The readouts can be native readouts. A native readout is one that does not rely on introduction of a reporter construct into the cell of interest. The readouts can be artificial. An artificial readout is one that relies on introduction of a reporter construct into the cell of interest. Examples of both are provided herein. In still other embodiments, a given assay may measure one or more native readouts and one or more artificial readouts. Each readout whether native or artificial is related to signaling pathways that ensue after TLR engagement with a ligand.

Each cell line described herein will be associated with a particular set of native readouts which the invention seeks to determine in the screening assays provided. As an example, the response of the RPMI 8226 cell line to an immunomodulatory molecule can be assessed in terms of native readouts such as CD71 expression, CD86 expression, HLA-DR

expression, IL-8 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF- α expression, TNF- α production and TNF- α secretion. RAMOS response can be assessed, inter alia, by CD80 cell surface expression. Raji response can be assessed, inter alia, by IL-6 secretion.

As described in greater detail herein, the cell line can be used in an unmodified form. In one respect, an unmodified cell line will naturally respond to a TLR ligand through a native readout system. For example, an RPMI 8226 cell exposed to an immunostimulatory TLR ligand may increase expression of IP-10 from the native gene locus. Alternatively, the cell line may be modified to contain a reporter construct that acts as a surrogate for the IP-10 gene locus. For example, the reporter construct may contain the TLR responsive promoter elements that are naturally found in the native IP-10 locus operably linked to a reporter coding sequence that encodes a gene product that is detectable and quantifiable. The structure and variability of suitable reporter constructs will be discussed in greater detail herein.

Readouts typically include the induction of a gene under control of a specific promoter such as a NF- κ B promoter. The gene under the control of the NF- κ B promoter can be a gene which naturally includes an NF- κ B promoter or it can be a gene in a construct in which an NF- κ B promoter has been inserted. Endogenous genes and transfected constructs which include the NF- κ B promoter include but are not limited to IL-8, IL-12 p40, NF- κ B-luc, IL-12 p40-luc, and TNF-luc.

Increases in cytokine levels can result from increased production, increased stability, increased secretion, or any combination of the foregoing, of the cytokine in response to the TLR-mediated signaling. Cytokines generally include, without limitation, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12, IL-13, IL-15, IL-18, IFN- α , IFN- β , IFN- γ , TNF- α , GM-CSF, G-CSF, M-CSF. Th1 cytokines include but are not limited to IL-2, IFN- γ , and IL-12. Th2 cytokines include but are not limited to IL-4, IL-5, and IL-10.

Increases in chemokine levels can result from increased production, increased stability, increased secretion, or any combination of the foregoing, of the chemokine in response to the TLR-mediated signaling. Chemokines of particular significance in the invention include but are not limited to CCL5 (RANTES), CXCL9 (Mig), CXCL10 (IP-10), CXCL11 (I-TAC), IL-8, and MCP-1.

TLR signaling activity can also be measured by phosphorylation, such as total cellular phosphorylation or phosphorylation of specific factors such as but not limited to IRAK, ERK, MyD88, TRAF6, p38, NF- κ B subunits, c-Jun and c-Fos.

TLR signaling activity can be measured by changes in gene expression. The
5 expression of CD71, CD86, CD80, CD69, CD54, HLA-DR, HLA class I, IL-6, IL-8, IL-10, IP-9, IP-10, IFN- α , TNF- α , and the like can be assessed as a measure of TLR signaling activity. Gene expression analysis may be performed using microarray techniques.

TLR signaling activity can also be measured by cell proliferation status or changes thereto.

10 TLR signaling activity can also be measured by cell surface marker expression such as the cell surface expression of markers such as but not limited to CD71, CD86, HLA-DR, CD80, HLA class I, CD54 and CD69.

TLR signaling activity can also be measured by antibody secretion such as but not limited to IgM secretion.

15

Reporter and Expression Constructs

The cells can be manipulated by the introduction of expression and/or reporter constructs. The expression constructs preferably comprise a TLR coding sequence, as described above. The reporter constructs can be used as surrogate measures of native TLR
20 signaling activity. These reporter constructs are intended to substitute for the "native" readouts capable with the cell line. In order to act as substitutes, the reporter constructs include a promoter element derived from a gene known to be modulated following TLR engagement with a TLR ligand. The reporter construct further includes a coding sequence linked to the promoter. The coding sequence is usually that of a reporter (i.e., a protein that is
25 detectable or quantifiable).

The reporter construct generally includes a promoter, a coding sequence and a polyadenylation signal. These nucleic acids shall include, as necessary, 5' non-transcribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, in addition to
30 promoter elements that are responsive to TLR signaling. The nucleic acid constructs may optionally include enhancer sequences or upstream activator sequences as desired.

The promoter in the reporter construct will include a TLR responsive promoter element, and will therefore be regarded as a TLR responsive promoter. As used herein, a

- 54 -

TLR responsive promoter is a promoter having an activity that is modulated (i.e., either activated or inhibited) by signaling through a TLR (e.g., by TLR interaction with its ligand). In order to be modulated by TLR signaling, the promoter contains sites that are bound by transcription factors modulated by TLR signaling. The factors may be activated or inhibited by TLR signaling. Activation of the transcription factor includes increases in the activity of the transcription factor per se, increases in its ability to interact with other factors or with DNA that serve to increase its activity, and increases in its transcription and translation (i.e., increased mRNA and protein levels of the transcription factor). Conversely, inhibition of the transcription factor includes decreases in the activity of the transcription factor per se, decreases in its ability to interact with other factors or with DNA that serve to decrease its activity, and decreases in its transcription and translation (i.e., decreased mRNA and protein levels of the transcription factor). The effect on the transcription factor is usually the downstream result of other interactions in the signaling pathway. The expression of coding sequences linked to such promoters will therefore be modulated by TLR signaling events, and it is the level of expression of these coding sequences that can be used as a readout of TLR signaling in the screening methods provided herein.

The TLR responsive promoter may comprise a transcription factor binding site selected from the group consisting of a NF- κ B binding site, an AP-1 binding site, a CRE, a SRE, an interferon-stimulated response element (ISRE), a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE, among others. These binding sites and their sequences are known in the art. Below is a exemplary list of these sequences.

W = A or T, R = A or G, Y = C or T

NF- κ B Binding site:

Consensus p50 subunit
5' GGGGATYCCC 3' (SEQ ID NO:90)

Consensus p65 subunit
5' GGGRNTTTC 3' (SEQ ID NO:91)

Example of p65 subunit binding site
5' AGT TGA GGG GAC TTT CCC AGG C 3' (SEQ ID NO:92)

CREB Binding site:
5'AGA GAT TGC CTG ACG TCA GAG AGC TAG 3' (SEQ ID NO:93)

- 55 -

AP-1 Binding site:

5'- CGC TTG ATG AGT CAG CCG GAA -3' (SEQ ID NO:94)

5'- CGC ATG AGT CAG ACA -3' (SEQ ID NO:95)

5 ISRE :

5'- TGCAGAAAGTGAAACTGAGG-3' (SEQ ID NO:96)

5'- AGAACGAAACA-3' (SEQ ID NO:97)

5'- GAGAAGTGAAAGTGG-3' (SEQ ID NO:98)

5'- TAAGAACATGAAACTGAA-3' (SEQ ID NO:99)

10 5'- ATGAAACTGAAAGTA-3' (SEQ ID NO:100)

5'- TGAAAACCGAAAGCGC-3' (SEQ ID NO:101)

5'- AGAAATGGAAAGT-3' (SEQ ID NO:102)

SRE

15 5'- TCACCCAC-3' (SEQ ID NO:103)

5'- CTCACCCAC-3' (SEQ ID NO:104)

5'- GCCACCCTAC-3' (SEQ ID NO:105)

NFAT:

20 5'- TATGAAACAGTTTTTCC -3' (SEQ ID NO:106)

5'- AGGAACTC -3' (SEQ ID NO:107)

5'- ARGARATTCC -3' (SEQ ID NO:108)

5'- CCAGTTGAGCCAGAGA -3' (SEQ ID NO:109)

25 GAS:

5'- CTTTCAGTTTCATATTACTCTAAATCCATT -3' (SEQ ID NO:110)

p53 Binding Site :

30 p53 Consensus site:

5'- RRRCWWGYYY -3' (SEQ ID NO:111)

Examples of p53 binding sites:

35 5'- AGGCATGCCT -3' (SEQ ID NO:112)

5'- GGGCTTGCCC -3' (SEQ ID NO:113)

5'- GGGCTTGCTT -3' (SEQ ID NO:114)

5'- GCCTGGACTTGCC -3' (SEQ ID NO:115)

5'- GGACATGCCCCGGGCATGTCC -3' (SEQ ID NO:116)

5'- GTAGCATTAGCCCAGACATGTCC -3' (SEQ ID NO:117)

40

TARE (TNF- α response element):

e.g. from the COL1A1 promoter

5'GAGGTATGCAGACAAGAGTCAGAGTTTCCCCTTGAA 3' (SEQ ID NO:118)

45

SRF

5'- CCWWWWWWGG -3' (SEQ ID NO:119)

5'- CCAAATAAGGC -3' (SEQ ID NO:120)

- 56 -

The TLR responsive promoter element can be derived from the promoter of a naturally occurring (i.e., an endogenous) gene that is activated or inhibited by TLR signaling (such as the IL-6 gene, the IL-8 gene, the IL-10 gene, the IL-12 p40 gene, the IP-9 gene, the IP-10 gene, the type 1 IFN gene, the IFN- α 4 gene, the IFN- β gene, the TNF- α gene, the TNF- β gene, the RANTES gene, the ITAC gene, the IGFBP4 gene, the CD54 gene, the CD69 gene, the CD71 gene, the CD80 gene, the CD86 gene, the HLA-DR gene, the HLA class I gene, and the like). The afore-mentioned genes are genes that are known to be activated in response to TLR interaction with its ligand.

Suitable promoter regions are described in the Examples. Briefly, the upstream (5') – 620 to +50 promoter region of IFN- α 4 or the upstream (5') –140 to +9 promoter region of IFN- α 1 can be used. In one embodiment, the IFN- α 4 sequence is cloned into the *Sma*I site of the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') promoter region of IFN- α 4.

The promoter can also be the upstream (5') –280 to +20 promoter region of IFN- β . The promoter can also be the upstream (5') –397 to +5 promoter region of RANTES. In one embodiment, the RANTES promoter sequence is cloned into the *Nhe*I site (filled in with Klenow) of the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') –397 to +5 promoter region of RANTES.

The promoter can also be the upstream truncated (-250 to +30) and full length (-860 to +30) promoter regions derived from human IL-12 p40 genomic DNA. In one embodiment, the truncated IL-12 p40 promoter was cloned as a *Kpn*I-*Xho*I insert into p β gal-Basic (Promega) resulting in an expression vector that includes a β gal gene under the control of the upstream (5') –250 to +30 promoter region of human IL-12 p40. In another embodiment, the full length IL-12 p40 promoter was cloned as a *Kpn*I-*Xho*I insert into p β gal-Basic (Promega) resulting in an expression vector that includes a β gal gene under the control of the upstream (5') –751 to +30 promoter region of human IL-12 p40. In another embodiment, the truncated –250 to +30 promoter region of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') –250 to +30 promoter region of human IL-12 p40. In yet another embodiment, the full length IL-12 p40 promoter of human IL-12 p40 was cloned into the

- 57 -

pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') -751 to +30 promoter region of human IL-12 p40.

The promoter can also be the upstream (5') -288 to +7 promoter region derived from human IL-6 genomic DNA. The promoter can also be derived from the full-length promoter
5 region of the IL-6 gene from -1174 to +7 (Accession No M22111, SEQ ID NO:129).

The promoter can also be the upstream (5') -734 to +44 or the upstream (5') -162 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71.

The promoter can also be derived from the -615 to +30 promoter region of human
10 TNF- α .

The promoter can also be derived from a promoter region of human TNF- β .

The promoter can also be derived from the -875 to +97 promoter region of human IP-
10.

The promoter can also be derived from the -219 to +114 promoter region of human
15 CXCL11 (IP9). The promoter can also be derived from the full length (-934 to +114) promoter region of human CXCL11 (IP9).

The promoter can also be derived from the -289 to +217 promoter region of human IGFBP4 (Insulin growth factor binding protein 4). The promoter can also be derived from the full length (-836 to +217) promoter region of human IGFBP4.

20 The promoter response element generally will be present in multiple copies, e.g., as tandem repeats. For example, in one reporter construct, coding sequence for luciferase is under control of an upstream 6X tandem repeat of NF- κ B response element. In another example, an ISRE-luciferase reporter construct useful in the invention is available from Stratagene (catalog no. 219092) and includes a 5x ISRE tandem repeat joined to a TATA box
25 upstream of a luciferase reporter gene.

The reporter construct coding sequence is preferably any nucleotide sequence that codes for a protein capable of detection or quantification. The protein can be an enzyme (e.g., luciferase, alkaline phosphatase, β -galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein
30 (GFP, U.S. Pat. No. 5,491,084), etc.), blue fluorescent protein (BFP, e.g., U.S. Pat. No. 6,486,382), etc.), a surface-expressed molecule (e.g., CD25, CD80, CD86), a secreted molecule (e.g., IL-1, IL-6, IL-8, IL-12 p40, TNF- α), a hapten or antigen, and other detectable protein products known to those of skill in the art. For assays relying on enzyme activity

- 58 -

readout, substrate can be supplied as part of the assay, and detection can involve measurement of chemiluminescence, fluorescence, color development, incorporation of radioactive label, drug resistance, or other marker of enzyme activity. For assays relying on surface expression of a molecule, detection can be accomplished using flow cytometry (FACS) analysis or functional assays. Secreted molecules can be assayed using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many of these and other suitable readout systems are well known in the art and are commercially available. Preferably, the coding sequence encodes a protein having a level or an activity that is quantifiable, preferably with a wide linear range.

The expression construct coding sequence is preferably a TLR coding sequence derived from the sequences listed herein. Preferably, the expression construct promoter is a constitutive promoter, although in some embodiments it may be inducible. Those of ordinary skill in the art are familiar with such promoters.

As used herein, a coding sequence and the regulatory sequences (such as promoters) are said to be operably linked when they are covalently linked in such a way as to place the expression or transcription and/or translation of the coding sequence under the influence or control of the regulatory sequence. Two DNA sequences are said to be operably linked if induction of a promoter in the 5' regulatory sequence results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a regulatory sequence would be operably linked to a coding sequence if the gene expression sequence were capable of effecting transcription of that coding sequence such that the resulting transcript is translated into the desired protein or polypeptide.

Methods for nucleic acid introduction into cells are known in the art.

The nucleic acid may be delivered to the cells alone or in association with a vector. In its broadest sense, a vector is any vehicle capable of facilitating the transfer of the nucleic acid to the cells so that the reporter can be expressed. The vector generally transports the nucleic acid to the cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In general, the vectors useful in the invention include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources that have been manipulated by the insertion or incorporation of the antigen nucleic acid sequences. Viral vectors are a preferred type of vector and include, but are not limited

- 59 -

to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus, Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known in the art.

Preferred viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high-efficiency transduction of genes *in vivo*. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell lined with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M., Gene Transfer and Expression, A Laboratory Manual W.H. Freeman C.O., New York (1990) and Murray, E.J. Methods in Molecular Biology, vol. 7, Humana Press, Inc., Clifton, New Jersey (1991).

A preferred virus for certain applications is the adeno-associated virus, a double-stranded DNA virus. The adeno-associated virus can be engineered to be replication-deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as, heat and lipid solvent stability; high transduction frequencies in cells of diverse lineages, including hemopoietic cells; and lack of superinfection inhibition thus allowing multiple series of transductions. Reportedly, wild-type adeno-associated virus manifest some preference for integration sites into human cellular DNA, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression characteristic of retroviral infection. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion.

Recombinant adeno-associated viruses that lack the replicase protein apparently lack this integration sequence specificity.

Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well-known to those of skill in the art. See e.g., Sambrook et al.,
5 Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been found to be particularly advantageous for delivering genes to cells *in vivo* because of their inability to replicate within and integrate into a host genome. These plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid.
10 Some commonly used plasmids include pBR322, pUC18, pUC19, pRc/CMV, SV40, and pBlueScript. Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids may be custom designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA.

In general, the vectors useful in the invention are divided into two classes: biological
15 vectors and chemical/physical vectors. Biological vectors and chemical/physical vectors are useful in the delivery and/or uptake of reporter constructs of the invention.

Most biological vectors are used for delivery of nucleic acids and thus would be most appropriate in the delivery of nucleic acids.

As used herein, a "chemical/physical vector" refers to a natural or synthetic molecule,
20 other than those derived from bacteriological or viral sources, capable of delivering the reference and test compound.

A preferred chemical/physical vector of the invention is a colloidal dispersion system. Colloidal dispersion systems include lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system of the invention is a
25 liposome. Liposomes are artificial membrane vessels which are useful as a delivery vector *in vivo* or *in vitro*. It has been shown that large unilamellar vessels (LUV), which range in size from 0.2 - 4.0 μm can encapsulate large macromolecules. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., *Trends Biochem. Sci.*, (1981) 6:77).

30 Liposomes may be targeted to a particular tissue by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Ligands which may be useful for targeting a liposome to an immune cell include, but are not limited to, intact or fragments of molecules which interact with immune cell specific receptors and molecules,

- 61 -

such as antibodies, which interact with the cell surface markers of immune cells. Such ligands may easily be identified by binding assays well known to those of skill in the art. In still other embodiments, the liposome may be targeted to the cancer by coupling it to a one of the immunotherapeutic antibodies discussed earlier. Additionally, the vector may be coupled
5 to a nuclear targeting peptide, which will direct the vector to the nucleus of the host cell.

Lipid formulations for transfection are commercially available from QIAGEN, for example, as EFFECTENE™ (a non-liposomal lipid with a special DNA condensing enhancer) and SUPERFECT™ (a novel acting dendrimeric technology).

Liposomes are commercially available from Gibco BRL, for example, as
10 LIPOFECTIN™ and LIPOFECTACE™, which are formed of cationic lipids such as N-[1-(2, 3 dioleyloxy)-propyl]-N, N, N-trimethylammonium chloride (DOTMA) and dimethyl dioctadecylammonium bromide (DDAB). Methods for making liposomes are well known in the art and have been described in many publications. Liposomes also have been reviewed by Gregoriadis, G. in *Trends in Biotechnology*, (1985) 3:235-241. In some preferred
15 embodiments, the method of choice for delivering DNA (for transfection) to the cells is electroporation, particularly where a stably transfected cell line is sought.

The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting.

20

Examples

Example 1. Biological Activity of Production Lot of CpG ODN (SEQ ID NO:1) Assayed Using Cells Stably Transfected with hTLR9 Expression Vector

CpG ODN (SEQ ID NO:1) is currently in preclinical and clinical trials for a number of
25 clinical applications. SEQ ID NO:1 has been discovered to induce signaling through TLR9. In order to assess different lots of clinical material, the methods of the invention are employed, using a highly characterized lot of SEQ ID NO:1 as a reference.

In a TLR9 assay, the CpG-non-responsive human embryonal kidney cell line HEK293 (e.g., ATCC CRL-1573) was stably transfected with a hTLR9 expression construct and found
30 to express full-length human TLR9 constitutively. The cells also contained a genomic copy of a reporter construct with a 6x NF-κB binding site and a luciferase gene reporter cassette. Incubation of the cells with CpG ODN (SEQ ID NO:1) activates NF-κB driven expression of luciferase, while incubation with medium alone (negative control) does not. The cells are

- 62 -

then lysed and activity of the luciferase protein determined by its catalytic activity of luciferin oxidation which is measured in a luminometer. Results are expressed as fold induction above medium control.

Assay set-up includes a reference standard material which is highly pure and well characterized. The reference material is used to create a standard curve within a defined range where the dose-response curve is linear (e.g., in the range of the EC50 value for SEQ ID NO:1, 70-100 nM). The test material is dissolved for testing and assayed at a defined concentration. Activity of the test material is calculated using the standard curve of the reference material. Quality of the tested material is deemed acceptable if activity of the test material compared to activity of the reference material falls within predetermined limits.

Example 2. Biological Activity of Production Lot of CpG ODN (SEQ ID NO:1) Assayed Using RPMI 8226 Cells

The assay of Example 1 is performed using RPMI 8226 cells (ATCC CCL-155) in place of the stably transfected HEK cells of Example 1. RPMI 8226 cells naturally express human TLR9. The cells are stably transfected with a 6x NF- κ B-luciferase reporter construct. It is to be understood that the assay could also be carried out by measuring a native readout such as IL-10 secretion.

Example 3. Expression Vectors for Human TLR3 (hTLR3) and Murine TLR3 (mTLR3)

To create an expression vector for human TLR3, human TLR3 cDNA was amplified by the polymerase chain method (PCR) from a cDNA made from human 293 cells using the primers 5'-GAAACTCGAGCCACCATGAGACAGACTTTGCCTTGTATCTAC-3' (sense, SEQ ID NO:152) and 5'-GAAAGAATTCTTAATGTACAGAGTTTTTGGATCCAAG-3' (antisense, SEQ ID NO:153). The primers introduce *Xho*I and *Eco*RI restriction endonuclease sites at their 5' ends for use in subsequent cloning into the expression vector. The resulting amplification product fragment was cloned into pGEM-T Easy vector (Promega), isolated, cut with *Xho*I and *Eco*RI restriction endonucleases, ligated into an *Xho*I/*Eco*RI-digested pcDNA3.1 expression vector (Invitrogen). The insert was fully sequenced and translated into protein. The cDNA sequence corresponds to the published cDNA sequence for hTLR3, available as GenBank accession no. NM_003265 (SEQ ID NO:7). The open reading frame codes for a protein 904 amino acids long, having the sequence corresponding to GenBank accession no. NP_003256 (SEQ ID NO:8).

Corresponding nucleotide and amino acid sequences for murine TLR3 (mTLR3) are known. The nucleotide sequence of mTLR3 cDNA has been reported as GenBank accession no. AF355152 (SEQ ID NO:9), and the amino acid sequence of mTLR3 has been reported as GenBank accession no. AAK26117 (SEQ ID NO:10).

5

Example 4. Reconstitution of TLR3 Signaling in 293 Fibroblasts

Human TLR3 cDNA and murine TLR3 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the *EcoRI* site. The resulting expression vectors mentioned above were transfected into
10 CpG-DNA non-responsive human 293 fibroblast cells (ATCC, CRL-1573) using the calcium phosphate method. Utilizing a "gain of function" assay it was possible to reconstitute human TLR3 (hTLR3) and murine TLR3 (mTLR3) signaling in 293 fibroblast cells.

Since NF- κ B activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-8; Muzio M et al. (1998) *J Exp Med*
15 187:2097-101), in a first set of experiments human 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and an NF- κ B-driven luciferase reporter construct.

Likewise, in a second set of experiments, 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and an IFN- α 4-driven luciferase reporter
20 construct (described in Example 8 below).

In a third group of experiments, 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and a RANTES-driven luciferase reporter construct (described in Example 14 below).

25 Example 5. Reconstitution of TLR7 Signaling

Methods for cloning murine and human TLR7 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated herein by reference. Human TLR7 cDNA and murine TLR7 cDNA in pT-Adv
30 vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the *EcoRI* site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR7 (hTLR7) and murine TLR7 (mTLR7) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors

mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

Example 6. Reconstitution of TLR8 Signaling

5 Methods for cloning murine and human TLR8 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated by reference. Human TLR8 cDNA and murine TLR8 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from
10 Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR8 (hTLR8) and murine TLR8 (mTLR8) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

15

Example 7. Reconstitution of TLR9 Signaling in 293 Fibroblasts

 Methods for cloning murine and human TLR9 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are
20 incorporated by reference. Human TLR9 cDNA and murine TLR9 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors
25 mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

 To generate stable clones expressing human TLR9, murine TLR9, or either TLR9 with the NF- κ B-luc reporter plasmid, 293 cells were transfected in 10 cm plates (2×10^6 cells/plate) with 16 μ g of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories GmbH, Cölbe,
30 Germany). Clones were tested for TLR9 expression by RT-PCR, for example as shown in Fig. 21. The clones were also screened for IL-8 production or NF- κ B-luciferase activity after stimulation with ODN. Four different types of clones were generated.

293-hTLR9-luc: expressing human TLR9 and 6x NF- κ B-luciferase reporter
 293-mTLR9-luc: expressing murine TLR9 and 6x NF- κ B-luciferase reporter
 293-hTLR9: expressing human TLR9
 293-mTLR9: expressing murine TLR9

5

Human 293 fibroblast cells were transiently transfected with hTLR9 and a 6x NF- κ B-luciferase reporter plasmid (NF- κ B-luc, kindly provided by Patrick Baeuerle, Munich, Germany) (Fig. 18A) or with hTLR9 alone (Fig. 18B). After stimulus with CpG-ODN (2 μ M, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:1), GpC-ODN (2 μ M, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:154), LPS (100 ng/ml) or media, NF- κ B activation by luciferase readout (8h, Fig. 18A) or IL-8 production by ELISA (48h, Fig. 18B) was monitored. Results are representative of three independent experiments. Fig. 18 shows that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

Human 293 fibroblast cells were transiently transfected with mTLR9 and the NF- κ B-luc construct. Similar data was obtained for IL-8 production (not shown). Thus expression of TLR9 (human or mouse) in 293 cells results in a gain of function for CpG DNA stimulation similar to hTLR4 reconstitution of LPS responses.

Figs. 19 and 20 demonstrate the responsiveness of a stable 293-mTLR9-luc and 293-hTLR9-luc clones after stimulation with CpG-ODN (2 μ M, SEQ ID NO:1), GpC-ODN (2 μ M, SEQ ID NO:154), Me-CpG-ODN (2 μ M; TZGTZGTTTTGTZGTTTTGTZGTT, Z = 5-methylcytidine, SEQ ID NO:147), LPS (100 ng/ml) or media, as measured by monitoring NF- κ B activation. Similar results were obtained utilizing IL-8 production with the stable clones. These results demonstrate that CpG-DNA non-responsive cell lines can be stably genetically complemented with TLR9 to become responsive to CpG DNA in a motif-specific manner.

25

Example 8. Method of Making IFN- α 4 Reporter Vector

A number of reporter vectors may be used in the practice of the invention. Some of the reporter vectors are commercially available, e.g., the luciferase reporter vectors pNF- κ B-Luc (Stratagene) and pAP1-Luc (Stratagene). These two reporter vectors place the luciferase gene under control of an upstream (5') promoter region derived from genomic DNA for NF- κ B or AP1, respectively. Other reporter vectors can be constructed following standard

30

- 66 -

methods using the desired promoter and a vector containing a suitable reporter, such as luciferase, β -galactosidase (β -gal), chloramphenicol acetyltransferase (CAT), and other reporters known by those skilled in the art. Following are some examples of reporter vectors constructed for use in the present invention.

5 IFN- α 4 is an immediate-early type 1 IFN. Sequence-specific PCR products for the -620 to +50 promoter region of IFN- α 4 were derived from genomic DNA of human 293 cells and cloned into the *Sma*I site of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -620 to +50 promoter region of IFN- α 4. The sequence of the -620 to +50 promoter region of IFN- α 4 is provided as
10 SEQ ID NO:121.

Example 9. Method of Making IFN- α 1 Reporter Vector

IFN- α 1 is a late type 1 IFN. Sequence-specific PCR products for the -140 to +9 promoter region of IFN- α 1 were derived from genomic DNA of human 293 cells and cloned
15 into *Sma*I site of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -140 to +9 promoter region of IFN- α 1. A sequence of the -140 to +9 promoter region of IFN- α 1 is provided as SEQ ID NO:122.

Example 10. Method of Making IFN- β Reporter Vector

20 IFN- β is an immediate-early type 1 IFN. The -280 to +20 promoter region of IFN- β was derived from the pUC β 26 vector (Algarte M et al. (1999) *J Virol* 73:2694-702) by restriction at *Eco*RI and *Taq*I sites. The 300 bp restriction fragment was filled in by Klenow enzyme and cloned into *Nhe*I-digested and filled in pGL3-Basic Vector (Promega). The
25 resulting expression vector includes a luciferase gene under control of an upstream (5') -280 to +20 promoter region of IFN- β . A sequence of the -280 to +20 promoter region of IFN- β is provided as SEQ ID NO:123.

Example 11. Method of Making Human IL-6 Reporter Vectors

Reporter constructs are made using the -285 to +7 promoter region derived from
30 human IL-6 genomic DNA. (Takeshita et al. Eur. J. Immunol. 2000. 30: 108-116.) In one reporter construct the IL-6 promoter region is cloned as a *Kpn*I-*Xho*I insert into pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of

- 67 -

an upstream (5') -288 to +7 promoter region derived from human IL-6 genomic DNA. A sequence of the -288 to +7 promoter region of human IL-6 is provided as SEQ ID NO:128.

The promoter can also be derived from the full-length promoter region of the IL-6 gene from -1174 to +7 (GenBank Accession No M22111) as shown below as SEQ ID
5 NO:129.

Example 12. Method of Making Human IL-8 Reporter Vectors

Reporter constructs have been made using a -546 to +44 and a truncated -133 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J*
10 *Immunol* 143:1366-71. In each reporter construct the IL-8 promoter region was cloned as a *KpnI-XhoI* insert into pGL3-Basic Vector (Promega). One of the resulting expression vectors includes a luciferase gene under control of an upstream (5') -546 to +44 promoter region derived from human IL-8 genomic DNA. Another of the resulting expression vectors includes a luciferase gene under control of an upstream (5') -133 to +44 promoter region
15 derived from human IL-8 genomic DNA.

The promoter can also be the upstream (5') -734 to +44 or the upstream (5') -162 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J*
Immunol 143:1366-71. A sequence of the -734 to +44 promoter region derived from human
; IL-8 is provided below as SEQ ID NO: 130.

20

Example 13. Method of Making Human IL-12 p40 Reporter Vectors

Reporter constructs have been made using truncated (-250 to +30, SEQ ID NO:127) and full length (-751 to +30, SEQ ID NO:126) promoter regions derived from human IL-12 p40 genomic DNA. (Takeshita et al. *Eur. J. Immunol.* 2000. 30: 108-116.) In one reporter
25 construct the truncated IL-12 p40 promoter was cloned as a *KpnI-XhoI* insert into pβgal-Basic (Promega). The resulting expression vector includes a β gal gene under control of an upstream (5') -250 to +30 promoter region of human IL-12 p40. In a second reporter construct the full length IL-12 p40 promoter was cloned as a *KpnI-XhoI* insert into pβgal-Basic (Promega). The resulting expression vector includes a β gal gene under control
30 of an upstream (5') -751 to +30 promoter region of human IL-12 p40. In a third reporter construct the truncated -250 to +30 promoter region of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -250 to +30 promoter region of human IL-12 p40. In a

- 68 -

fourth reporter construct the full length IL-12 p40 promoter of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -751 to +30 promoter region of human IL-12 p40. A sequence of the -751 to +30 promoter region of human IL-12 p40 is provided as SEQ ID NO: 126.

Example 14. Method of Making RANTES Reporter Vector

Transcription of the chemokine RANTES is believed to be regulated at least in part by IRF3 and by NF- κ B. Lin R et al. (1999) *J Mol Cell Biol* 19(2):959-66; Genin P et al. (2000) *J Immunol* 164:5352-61. A 483 bp sequence-specific PCR product including the -397 to +5 promoter region of RANTES was derived from genomic DNA of human 293 cells, restricted with *Pst*I and cloned into pCAT-Basic Vector (Promega) using *Hind*III (filled in with Klenow) and *Pst*I sites (filled in). The -397 to +5 promoter region of RANTES was then isolated from the resulting RANTES/chloramphenicol acetyltransferase (CAT) reporter plasmid by restriction with *Bgl*II and *Sal*I, filled in with Klenow enzyme, and cloned into the *Nhe*I site (filled in with Klenow) of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') -397 to +5 promoter region of RANTES. Comparison of the insert sequence -397 to +5 of Genin P et al. (2000) *J Immunol* 164:5352-61 and GenBank accession no. AB023652 (SEQ ID NO:125) revealed two point deletions (at positions 105 and 273 of SEQ ID NO:125) which do not create new restriction sites. A sequence of the -397 to +5 promoter region of RANTES is provided as SEQ ID NO:125.

Example 15. RT-PCR Analysis of Cell Lines for TLR Expression

TLR expression was determined using total RNA of cells prepared by standard methods (QIAGEN). RNA was transcribed to cDNA using AMV Reverse Transcriptase (Roche). Quantitative PCR was performed with TLR-gene specific primer sets using a LightCycler Instrument (Roche). Controls for genomic DNA impurities were performed by a similar PCR method using RNA (but without reverse transcriptase).

A variety of cell lines was screened for their expression of TLR3, 7, 8 and 9. These cell lines are A549 (human lung carcinoma), BeWo (human choriocarcinoma), HeLa (human cervix carcinoma), Hep-2 (human cervix carcinoma), KG-1 (human acute myeloid leukemia), MUTZ-3 (human acute myelomonocytic leukemia), Nalm-6 (human B cell precursor

leukemia), NK-92 (human Natural killer cell line), NK-92 MI (human Natural killer cell line, IL-2 independent), Raji (human Burkitt's lymphoma, B lymphocyte), RAMOS (Burkitt's lymphoma, B lymphocyte), RPMI 8226 (human multiple myeloma, B lymphocyte), THP-1 (human acute monocytic leukemia), U937 (human lymphoma) and Jurkat (human T cell
 5 leukemia).

All B cell lines express, as determined by Real Time-PCR (RT-PCR), endogenous TLR9. In addition, all lines except NALM co-express TLR7. Nevertheless, none of the other cell lines appeared to express TLR7, whereas low TLR9 expression on the mRNA level was observed for KG-1 and THP-1. TLR3 appeared to be expressed in most of these cell lines,
 10 with the highest mRNA levels for example in the NK cell lines (e.g., NK-92).

Raji cells contain high levels of TLR9 mRNA and low levels of TLR3 and TLR7 mRNA suggesting high expression of TLR9 protein and lower levels of TLR3 and TLR7 protein.

These results indicate that the cell lines expressing TLR9 can be used to screen
 15 potential new TLR9 ligands (CpG ODN, etc.), cell lines expressing TLR7 to screen potential new TLR7 ligands (ORN (oligoribonucleotides), small molecules, etc.), and cell lines expressing both receptors may be used to screen for "hybrid" TLR7 and 9 agonists. In addition, cell lines lacking TLR8 expression (i.e., all cell lines tested) can be used to confirm the specificity of a TLR7 versus a TLR8 ligand (i.e., the latter should not be able to stimulate
 20 TLR7-expressing cells). In contrast, cell lines expressing TLR3 (e.g., Raji cells) may be used to screen for potential new TLR3 ligands (dsRNA, etc.).

Example 16. Screening of Various Cell Lines for Responses to TLR Ligands

Except where otherwise indicated, the following general methods were used.
 25 Cells were plated at 5×10^5 /ml in 48 well plates in RPMI medium with 10% FBS. Stimulation was performed by addition of the oligonucleotides or other compounds diluted to the test concentrations in TE. Cells were incubated for 24 or 48h and the supernatants were taken to analyse for the presence of cytokines or chemokines.

The TLR ligands used are as follows:

30 TLR3: Poly I:C

TLR7, TLR8: R-848

TLR9:

T*C*C*A*G*G*A*C*T*T*C*T*C*T*C*A*G*G*T*T (SEQ ID NO: 2);

- 70 -

- T*C*G*T*C*G*T*T*T*T*G*T*C*G*T*T*T*G*T*C*G*T*T (SEQ ID NO: 1);
 T*G*C*T*G*C*T*T*T*T*G*T*G*C*T*T*T*G*T*G*C*T*T (SEQ ID NO: 154);
 T*C*G*T*C*G*T*T*T*T*C*G*G*C*G*C*G*C*G*C*G (SEQ ID NO: 158);
 G*G*G_G_A_C_G_A_C_G_T_C_G_T_G_G*G*G*G*G*G (SEQ ID NO: 159);
 5 T*G*C*T*G*C*T*T*T*T*C*G*G*C*G*G*C*G*C*G (SEQ ID NO: 160);
 G*G*G_G_A_G_C_A_G_C_T_G_C_T_G_G*G*G*G*G*G (SEQ ID NO: 161).
 * phosphorothioate linkage; _ phosphodiester linkage.

Increased expression of cell surface markers was determined using cells stimulated as
 10 described above and then stained with different monoclonal antibody combinations specific
 for the cell surface markers. Analysis of the cells was performed by flow cytometry.

Changes in reporter gene activity were determined using cells transfected with a
 NF- κ B reporter construct (Stratagene) and a β -galactosidase reporter control plasmid
 (Invitrogen) using electroporation. For NF- κ B analysis, a 5x NF- κ B-Luciferase Vector
 15 (Stratagene) was used. The amount of DNA transfected as well as cell concentration was
 varied. Stimulation was performed 24h after transfection. Cells were stimulated with the
 indicated amounts of ODN, R-848, LPS, TNF- α , or IL-1 β for the indicated incubation times.
 Cell extracts were prepared by lysing the cells in 100 μ l reporter lysis buffer (Promega) using
 the freeze-thaw method. All data were normalized for β -galactosidase expression.
 20 Stimulation indices were calculated in reference to luciferase activity of medium without
 addition of ODN.

Stimulation of the Raji cell line with a TLR9 ligand (CpG ODN), a TLR3 ligand (poly
 I:C) or a TLR7 ligand (R-848) results in the ligand-specific secretion of cytokines. Figs. 14
 and 15 show IL-6 production of Raji cells upon stimulation with ODN, poly I:C or R-848.
 25 Fig. 16 shows IFN- α 2 production of Raji cells upon stimulation with ODN, poly I:C or R-848.
 In all assays, cells were incubated with Na-Butyrate for 48h before stimulation with TLR
 ligands. CpG stimulation of the RAMOS cell lines can result in the CpG-specific up-
 regulation of cell surface markers such as CD80, as shown in Fig. 17.

30 Example 17. Inhibition of a Positive Reference Compound Response with an Inhibitory Test Compound

Inhibition of CpG mediated chemokine production was determined using RPMI 8226
 cells incubated with increasing amounts of SEQ ID NO:1 in the presence of an

- 71 -

immunoinhibitory ODN (SEQ ID NO: 151). IP-10 production was measured 24h later by ELISA (Fig. 9).

Equivalents

5 The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described
10 herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

 All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

15

We claim:

- 72 -

Claims

1. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising
contacting an RPMI 8226 cell that expresses a TLR with a test compound and
5 measuring a test level of TLR signaling activity,
wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and
wherein the TLR signaling activity is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-8 production, IL-8
10 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF- α expression, TNF- α production and TNF- α secretion.
2. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising
15 contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,
wherein a test level that is positive is indicative of an immunostimulatory compound, and
wherein the cell is a Raji cell, a RAMOS cell, a Nalm cell, a THP-1 cell, or a KG-
20 1 cell.
3. The method of claim 1 or 2, wherein the test level is positive relative to a reference level determined by contacting the cell with a reference compound and measuring a reference TLR signaling activity.
25
4. The method of claim 3, wherein the reference compound is a positive reference compound
5. The method of claim 4, wherein the positive reference compound is
30 selected from the group consisting of an immunostimulatory nucleic acid and an imidazoquinoline compound.

- 73 -

6. The method of claim 3, wherein the reference compound is a negative reference compound.

7. The method of claim 6, wherein the negative reference compound is
5 medium alone.

8. The method of claim 5, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

10

9. The method of claim 5, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

10. The method of claim 1 or 2, wherein the test compound is a nucleic
15 acid.

11. The method of claim 10, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

20

12. The method of claim 10, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

13. The method of claim 10, wherein the nucleic acid is a DNA, an RNA or
25 a DNA-RNA hybrid.

14. The method of claim 1 or 2, wherein the test compound is a non-nucleic acid small molecule.

15. The method of claim 1 or 2, wherein the test compound comprises an
30 amino acid, a carbohydrate, a lipid, or a hormone.

16. The method of claim 15, wherein the carbohydrate is a polysaccharide.

- 74 -

17. The method of claim 1 or 2, wherein the test compound is derived from a molecular library.
- 5 18. The method of claim 1, wherein the cell is transfected with a nucleic acid.
19. The method of claim 18, wherein the nucleic acid encodes a TLR or a reporter construct.
- 10 20. The method of claim 2, wherein the cell is transfected with a nucleic acid.
21. The method of claim 20, wherein the nucleic acid encodes a TLR or a reporter construct.
- 15 22. The method of claim 19 or 21, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.
- 20 23. The method of claim 22, wherein the TLR is a human TLR.
24. The method of claim 19 or 21, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a β -galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.
- 25 25. The method of claim 19 or 21, wherein the reporter construct comprises a TLR responsive promoter.
- 30 26. The method of claim 25, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of a NF- κ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an

- 75 -

IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

27. The method of claim 25, wherein the TLR responsive promoter is a
5 promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN- α 1 promoter region, an IFN- α 4 promoter region, an IFN- β promoter region, an IFN- γ promoter region, a TNF- α promoter region, a TNF- β promoter region, an IP-9 promoter region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a
10 MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

28. The method of claim 18 or 20, wherein the cell is stably transfected.
15

29. The method of claim 1 or 2, wherein the TLR signaling activity is measured by cytokine secretion or chemokine secretion.

30. The method of claim 1, wherein the TLR signaling activity is selected
20 from the group consisting of IL-8 secretion, IL-10 secretion, IP-10 secretion and TNF- α secretion.

31. The method of claim 2, wherein the TLR signaling activity is selected
from the group consisting of IL-6 expression, IL-6 production, IL-6 secretion, IL-8
25 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, IL-12 expression, IL-12 production, IL-12 secretion, TNF- α expression, TNF- α production and TNF- α secretion.

32. The method of claim 2, wherein the TLR signaling activity is measured
30 by phosphorylation.

33. The method of claim 32, wherein phosphorylation is total cellular phosphorylation.

- 76 -

34. The method of claim 32, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NFkB subunits, c-Jun and c-Fos.

5

35. The method of claim 1 or 2, wherein the TLR signaling activity is measured by gene expression.

36. The method of claim 1, wherein the TLR signaling activity is measured by gene expression selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-10 expression, IP-10 expression, and TNF- α expression.

37. The method of claim 35, wherein TLR signaling activity is measured by microarray techniques.

38. The method of claim 2, wherein the TLR signaling activity is measured by cell proliferation.

39. The method of claim 1 or 2, wherein TLR signaling activity is measured by cell surface marker expression.

40. The method of claim 1, wherein TLR signaling activity is measured by cell surface expression of CD71, CD86 or HLA-DR.

25

41. The method of claim 2, wherein TLR signaling activity is measured by CD71 cell surface expression, CD86 cell surface expression, HLA-DR cell surface expression, CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

30

42. The method of claim 2, wherein TLR signaling activity is measured by antibody secretion.

- 77 -

43. The method of claim 42, wherein the antibody secretion is IgM secretion.

44. A composition comprising
an RPMI 8226 cell stably transfected with a nucleic acid encoding a TLR
5 polypeptide, or a fragment thereof.

45. The composition of claim 44, further comprising a reporter construct
comprising a promoter and a reporter sequence wherein the promoter is a TLR responsive
promoter.

10

46. The composition of claim 45, wherein the TLR responsive promoter
comprises a nucleic acid sequence selected from the group consisting of an NF- κ B binding
site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3
binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding
15 site, and a TARE.

47. The composition of claim 45, wherein the reporter sequence is selected
from the group consisting of a luciferase sequence, a β -galactosidase sequence, a green
fluorescent protein sequence, a secreted alkaline phosphatase sequence and a chloramphenicol
20 transferase sequence.

48. The composition of claim 44, wherein the TLR polypeptide or fragment
thereof is a human TLR polypeptide or fragment thereof.

25 49. The composition of claim 44, wherein the TLR polypeptide or fragment
thereof is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6,
TLR7, TLR8, TLR9 and TLR10.

50. The composition of claim 44, wherein the TLR polypeptide or fragment
30 thereof is a human TLR polypeptide.

51. A screening method for identifying agonists of Toll-like receptor (TLR)
signaling activity, comprising

- 78 -

contacting an cell that ectopically expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

5 wherein the cell that ectopically expresses a TLR is selected from the group consisting of RPMI 8226, RAMOS, Raji, Nalm, THP-1, KG-1 and 293 HEK.

52. The method of claim 51, wherein the test level is positive relative to a reference level determined by contacting the cell with a reference compound and measuring a
10 reference TLR signaling activity.

53. The method of claim 52, wherein the reference compound is a positive reference compound.

15 54. The method of claim 53, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an imidazoquinoline compound.

55. The method of claim 54, wherein the immunostimulatory nucleic acid
20 is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

56. The method of claim 54, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

25

57. The method of claim 52, wherein the reference compound is negative reference compound.

58. The method of claim 57, wherein the negative reference compound is
30 medium alone.

59. The method of claim 51, wherein the test compound is a nucleic acid.

- 79 -

60. The method of claim 59, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.
- 5 61. The method of claim 59, wherein the nucleic acid comprises a phosphorothioate backbone linkage.
62. The method of claim 59, wherein the nucleic acid is a DNA, an RNA, or a DNA-RNA hybrid.
- 10 63. The method of claim 51, wherein the test compound is a non-nucleic acid small molecule.
64. The method of claim 51, wherein the test compound comprises an
15 amino acid, a carbohydrate, a lipid, or a hormone.
65. The method of claim 64, wherein the carbohydrate is a polysaccharide.
66. The method of claim 51, wherein the test compound is derived from a
20 molecular library.
67. The method of claim 51, wherein the TLR signaling activity is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-6 expression, IL-6 production, IL-6 secretion, IL-8 expression, IL-8 production, IL-8 secretion,
25 IL-10 expression, IL-10 production, IL-10 secretion, IL-12 expression, IL-12 production, IL-12 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF- α expression, TNF- α production and TNF- α secretion.
68. The method of claim 51, wherein the TLR is selected from the group
30 consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.
69. The method of claim 51, wherein the TLR is a human TLR.

- 80 -

70. The method of claim 51, wherein the cell is transfected with a reporter construct.

71. The method of claim 70, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a β -galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.

72. The method of claim 71, wherein the TLR signaling activity is measured by luciferase expression, β -galactosidase expression, chloramphenicol expression, acetyltransferase expression, green fluorescent protein expression, alkaline phosphatase expression and alkaline phosphatase secretion.

73. The method of claim 71, wherein the reporter construct comprises a TLR responsive promoter.

74. The method of claim 25 or 73, wherein the TLR responsive promoter is a TLR1 responsive promoter, a TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter and a TLR10 responsive promoter.

75. The method of claim 73, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of an NF- κ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

76. The method of claim 73, wherein the TLR responsive promoter is a promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN- α 1 promoter region, an IFN- α 4 promoter region, an IFN- β promoter region, an IFN- γ promoter region, a TNF- α promoter region, a TNF- β promoter region, an IP-9 promoter

- 81 -

region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

5

77. The method of claim 51, wherein the cell is stably transfected with a TLR nucleic acid.

78. The method of claim 70, wherein the cell is stably transfected with the
10 reporter construct.

79. The method of claim 51, wherein the TLR signaling activity is measured by cytokine secretion or chemokine secretion.

80. The method of claim 79, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-8 secretion, TNF- α secretion, IL-10 secretion and IP-10 secretion.

81. The method of claim 79, wherein the cytokine secretion or chemokine
20 secretion is selected from the group consisting of IL-6 secretion and IL-12 secretion.

82. The method of claim 51, wherein the TLR signaling activity is measured by phosphorylation.

83. The method of claim 82, wherein phosphorylation is total cellular
25 phosphorylation.

84. The method of claim 82, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NF- κ B
30 subunits, c-Jun and c-Fos.

85. The method of claim 51, wherein the TLR signaling activity is measured by gene expression.

86. The method of claim 85, wherein the gene expression is selected from the group consisting of IL-8 expression, IL-10 expression, IP-10 expression, CD71 expression, CD86 expression and HLA-DR expression.

5

87. The method of claim 85, wherein the gene expression is selected from the group consisting of IL-6 expression, IL-12 expression and TNF- α expression.

88. The method of claim 51, wherein the TLR signaling activity is
10 measured by microarray techniques.

89. The method of claim 51, wherein the TLR signaling activity is measured by cell proliferation.

90. The method of claim 51, wherein the TLR signaling activity is
15 measured by cell surface marker expression.

91. The method of claim 90, wherein the cell surface marker expression is selected from the group consisting of CD71 cell surface expression, CD86 cell surface
20 expression and HLA-DR cell surface expression.

92. The method of claim 90, wherein the cell surface marker expression is selected from the group consisting of CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

25

93. The method of claim 51, wherein the TLR signaling activity is measured by antibody secretion.

94. The method of claim 93, wherein the antibody secretion is IgM
30 secretion.

95. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

- 83 -

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

5 wherein a test level that is less than a reference level is indicative of test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell, a Raji cell, a THP-1 cell, a Nalm cell and a KG-1 cell.

10 96. The method of claim 95, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an immunostimulatory imidazoquinoline compound.

15 97. The method of claim 96, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

98. The method of claim 96, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

20 99. The method of claim 95, wherein the test compound is a nucleic acid.

100. The method of claim 99, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

101. The method of claim 99, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

30 102. The method of claim 99, wherein the nucleic acid is a DNA, an RNA or a DNA-RNA hybrid.

- 84 -

103. The method of claim 95, wherein the test compound is a non-nucleic acid small molecule.

104. The method of claim 95, wherein the test compound comprises an amino acid, a carbohydrate, a lipid, or a hormone.

105. The method of claim 104, wherein the carbohydrate is a polysaccharide.

106. The method of claim 95, wherein the test compound is derived from a molecular library.

107. The method of claim 95, wherein the experimental cell is transfected with a nucleic acid.

108. The method of claim 107, wherein the nucleic acid encodes a TLR or a reporter construct.

109. The method of claim 108, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.

110. The method of claim 108, wherein the TLR is a human TLR.

111. The method of claim 108, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a β -galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.

112. The method of claim 111, wherein the TLR signaling activity is selected from the group consisting of luciferase expression, β -galactosidase expression, chloramphenicol acetyltransferase expression, green fluorescent protein expression, alkaline phosphatase expression and alkaline phosphatase secretion.

- 85 -

113. The method of claim 108, wherein the reporter construct comprises a TLR responsive promoter.

114. The method of claim 113, wherein the TLR responsive promoter
5 comprises a transcription factor binding site selected from the group consisting of an NF- κ B binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

115. The method of claim 113, wherein the TLR responsive promoter is a
10 promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN- α 1 promoter region, an IFN- α 4 promoter region, an IFN- β promoter region, an IFN- γ promoter region, a TNF- α promoter region, a TNF- β promoter region, an IP-9 promoter
15 region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

116. The method of claim 113, wherein the TLR responsive promoter is
20 selected from the group consisting of a TLR1 responsive promoter, TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter and a TLR10 responsive promoter.

25

117. The method of claim 107, wherein the cell is stably transfected with the nucleic acid.

118. The method of claim 95, wherein the TLR signaling activity is
30 measured by cytokine secretion or chemokine secretion.

- 86 -

119. The method of claim 118, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-6 secretion, IL-12 secretion and TNF- α secretion.

5 120. The method of claim 118, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-8 secretion, IL-10 secretion and IP-10 secretion.

121. The method of claim 95, wherein the TLR signaling activity is
10 measured by phosphorylation.

122. The method of claim 121, wherein phosphorylation is total cellular phosphorylation.

15 123. The method of claim 122, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NF- κ B subunits, c-Jun and c-Fos.

124. The method of claim 95, wherein the TLR signaling activity is
20 measured by gene expression.

125. The method of claim 124, wherein the gene expression is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-10 expression and IP-10 expression.

25 126. The method of claim 124, wherein the gene expression is selected from the group consisting of IL-6 expression, IL-12 expression and TNF- α expression.

127. The method of claim 95, wherein the TLR signaling activity is
30 measured by microarray techniques.

128. The method of claim 95, wherein the TLR signaling activity is measured by cell proliferation.

129. The method of claim 95, wherein the TLR signaling activity is measured by cell surface marker expression.

5 130. The method of claim 129, wherein the cell surface marker expression is selected from the group consisting of CD71 cell surface expression, CD86 cell surface expression and HLA-DR MHC class II cell surface expression.

10 131. The method of claim 129, wherein the cell surface marker expression is selected from the group consisting of CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

15 132. The method of claim 95, wherein the TLR signaling activity is measured by antibody secretion.

133. The method of claim 132, wherein the antibody secretion is IgM secretion.

20 134. The method of claim 95, wherein the cell is contacted to the positive reference compound and the test compound simultaneously.

135. The method of claim 95, wherein the cell is contacted to the positive reference compound prior to contact with the test compound.

25 136. The method of claim 95, wherein the cell is contacted to the test compound prior to contact with the positive reference compound.

30 137. A method for quality assessment of a test composition containing a known Toll like receptor (TLR) ligand, comprising:
measuring a reference activity of a reference composition comprising a known TLR ligand, wherein the known TLR ligand is a nucleic acid molecule;
measuring a test activity of a test composition comprising the known TLR ligand; and
comparing the test activity to the reference activity.

138. The method of claim 137, further comprising selecting the test composition if the test activity falls within a predetermined range of variance about the reference activity.

5

139. The method of claim 1, wherein the reference composition is a first production lot of a pharmaceutical composition comprising the known TLR ligand, and wherein the test composition is a second production lot of a pharmaceutical composition comprising the known TLR ligand.

10

140. The method of claim 137, wherein the reference composition is a first in-process lot of a composition comprising the known TLR ligand, and wherein the test composition is a second in-process lot of a composition comprising the known TLR ligand.

15

141. The method of claim 137, wherein the measuring the reference activity comprises contacting the reference composition with an isolated cell expressing a TLR responsive to the known TLR ligand, and wherein the measuring the test activity comprises contacting the test composition with the isolated cell expressing a TLR responsive to the known TLR ligand.

20

142. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand comprises an expression vector for the TLR responsive to the known TLR ligand.

25

143. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand naturally expresses the TLR responsive to the known TLR ligand.

30

144. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226.

- 89 -

145. The method of claim 137, wherein the measuring the reference activity and the measuring the test activity each comprise measuring signaling activity mediated by a TLR responsive to the known TLR ligand.

5 146. The method of claim 145, wherein the signaling activity is activity of a reporter construct under control of NF- κ B response element.

147. The method of claim 145, wherein the signaling activity is activity of a reporter construct under control of interferon-stimulated response element (ISRE).

10

148. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IFN- α promoter.

149. The method of claim 145, wherein the signaling activity is activity of a
15 reporter gene under control of an IFN- β promoter.

150. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-6 promoter.

20 151. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-8 promoter.

152. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-12 p40 promoter.

25

153. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of a RANTES promoter.

154. The method of claim 137, wherein the known TLR ligand is a TLR9
30 ligand.

155. The method of claim 137, wherein the known TLR ligand is a TLR3 ligand.

- 90 -

156. The method of claim 137, wherein the known TLR ligand is a TLR7 ligand.

5 157. The method of claim 137, wherein the known TLR ligand is a TLR8 ligand.

158. The method of claim 137, wherein the known TLR ligand is an immunostimulatory nucleic acid.

10 159. The method of claim 137, wherein the known TLR ligand is a CpG nucleic acid.

15 160. The method of claim 137, wherein the known TLR ligand is an immunoinhibitory nucleic acid.

161. A method for quality assessment of a test lot of a pharmaceutical product containing a known TLR9 ligand, comprising:
measuring a reference activity of a reference lot of a pharmaceutical product
20 comprising a known TLR9 ligand, wherein the known TLR9 ligand is a nucleic acid molecule;
measuring a test activity of a test lot of a pharmaceutical product comprising the known TLR9 ligand;
comparing the test activity to the reference activity; and
25 rejecting the test lot if the test activity falls outside of a predetermined range of variance about the reference activity.

162. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID
30 NO:1).

- 91 -

163. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTGACGTTTTGTCGTT-3' (SEQ ID NO:139).

5 164. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTGTCGTTTTTTTCGA-3' (SEQ ID NO:140).

165. The method of claim 161, wherein the known TLR9 ligand is an
10 oligonucleotide comprising a base sequence 5'-TCGTCGTTTCGTCGTTTCGTCGTT-3' (SEQ ID NO:141).

166. The method of claim 161, wherein the known TLR9 ligand is an
15 oligonucleotide comprising a base sequence 5'-TCGTCGTTTCGTCGTTTTGTCGTT-3' (SEQ ID NO:142).

167. The method of claim 161, wherein the known TLR9 ligand is an
oligonucleotide comprising a base sequence 5'-TCGTCGTTTTTCGGTCGTTTT-3' (SEQ ID
20 NO:143).

168. The method of claim 161, wherein the known TLR9 ligand is an
oligonucleotide comprising a base sequence 5'-TCGTCGTTTTTCGTGCGTTTTT-3' (SEQ
ID NO:144).

25 169. The method of claim 161, wherein the known TLR9 ligand is an
oligonucleotide comprising a base sequence 5'-TCGTCGTTTTCGGCGGCCGCCG-3' (SEQ
ID NO:145).

170. The method of claim 161, wherein the known TLR9 ligand is an
30 oligonucleotide comprising a base sequence 5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3'
(SEQ ID NO:146), wherein every internucleoside linkage is phosphorothioate except for
those indicated by “_”, which are phosphodiester.

- 92 -

171. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

5 wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell, a RAMOS cell, a Nalm cell, a THP-1 cell, or a KG-1 cell, and the TLR is TLR9.

10 172. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

15 wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell or a RAMOS cell, and the TLR is TLR7.

173. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

20 contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

25 wherein the cell is a Raji cell, a RAMOS cell, a KG-1 cell, a Nalm-6 cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell, and the TLR is TLR3.

174. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

30 contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

- 93 -

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell, a Raji cell, a THP-1 cell, a Nalm cell and a KG-1 cell, and the TLR is TLR9.

5

175. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

10 contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

15 wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell and a Raji cell, and the TLR is TLR7.

175. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

20 contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

25 wherein the cell is selected from the group consisting of a Raji cell, a RAMOS cell, a KG-1 cell, a Nalm-6 cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell and an NK-92 MI cell, and the TLR is TLR3.

176. A screening method for identifying an enhancer of a Toll-like receptor (TLR) agonist, comprising

30 contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity, and

contacting a cell with the positive reference compound and a test compound and measuring a test level of TLR signaling activity,

wherein the positive reference compound is a TLR agonist, and a test level that is greater than the reference level is indicative of a test compound that is an enhancer of a TLR agonist.

177. The method of claim 176, wherein the positive reference compound is an immunostimulatory nucleic acid.

178. The method of claim 176, wherein the positive reference compound is an imidazoquinoline compound.

180. The method of claim 176, wherein the cell is selected from the group consisting of a KG-1 cell, a Nalm-6 cell, a Raji cell, a RAMOS cell, a Jurkat cell, a HeLa cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell and an NK-92 MI cell, and the TLR is TLR3.

181. The method of claim 176, wherein the cell is selected from the group consisting of a KG-1 cell, a Nalm-6 cell, a Raji cell, an RPMI 8226 cell, a RAMOS cell, and a THP-1 cell, and the TLR is TLR9.

182. The method of claim 176, wherein the cell is selected from the group consisting of a Raji cell, an RPMI 8226 cell and a RAMOS cell, and the TLR is TLR7.

183. The method of claim 1, wherein the TLR is TLR7 or TLR9.

184. The method of claim 172-175 or 176, wherein the cell is unmodified.

1/15

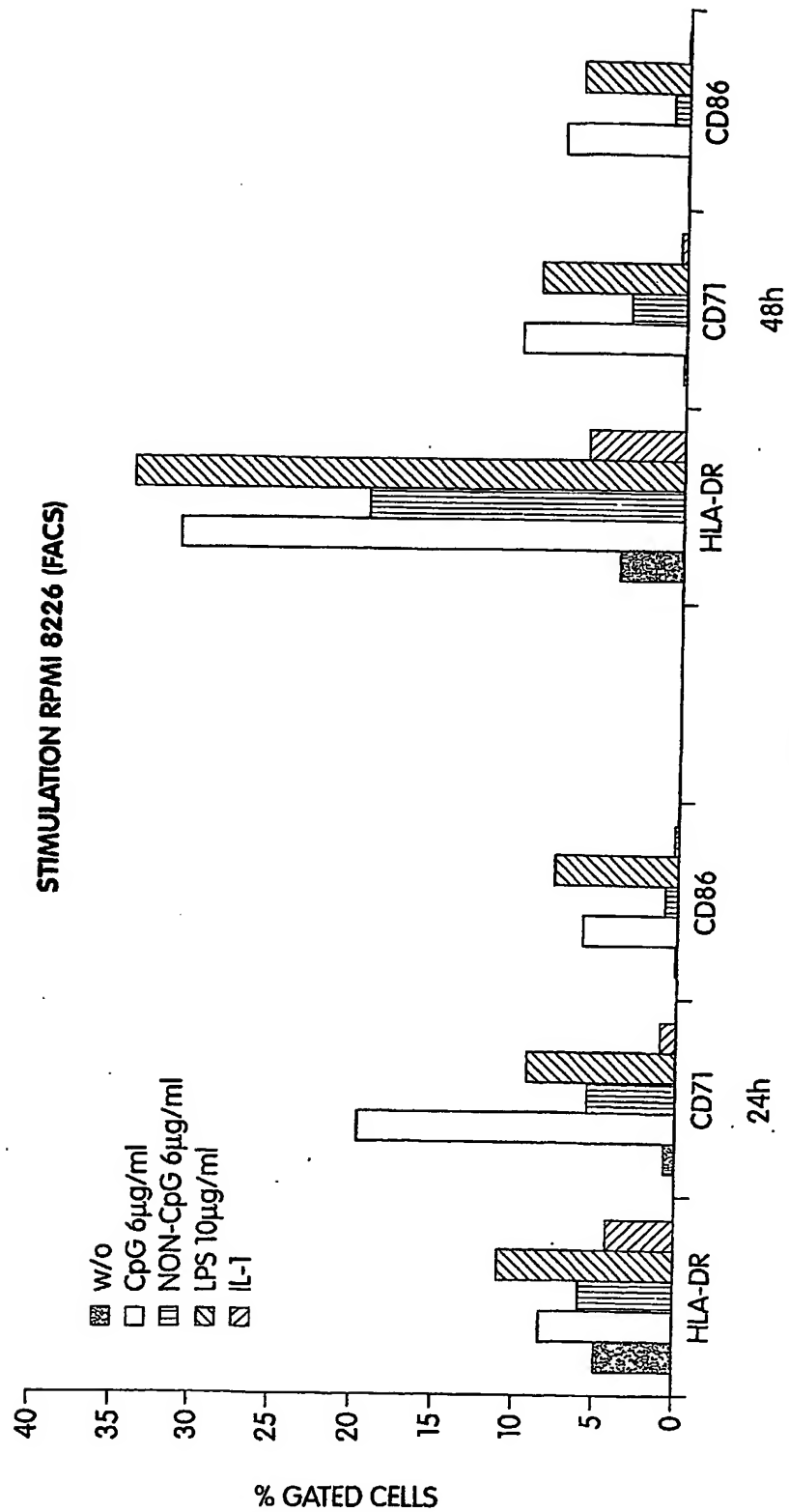


Fig. 1

2/15

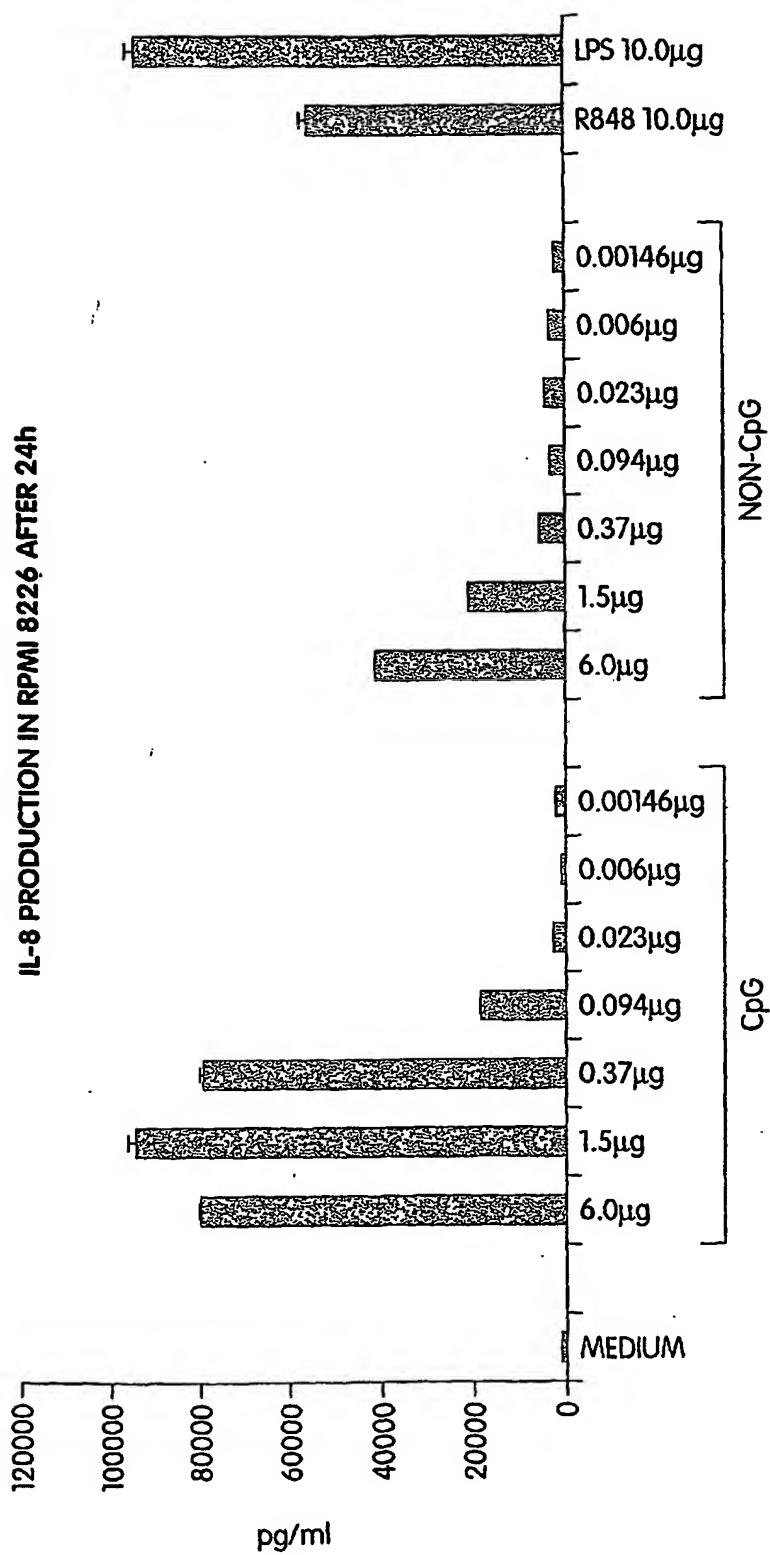


Fig. 2

3/15

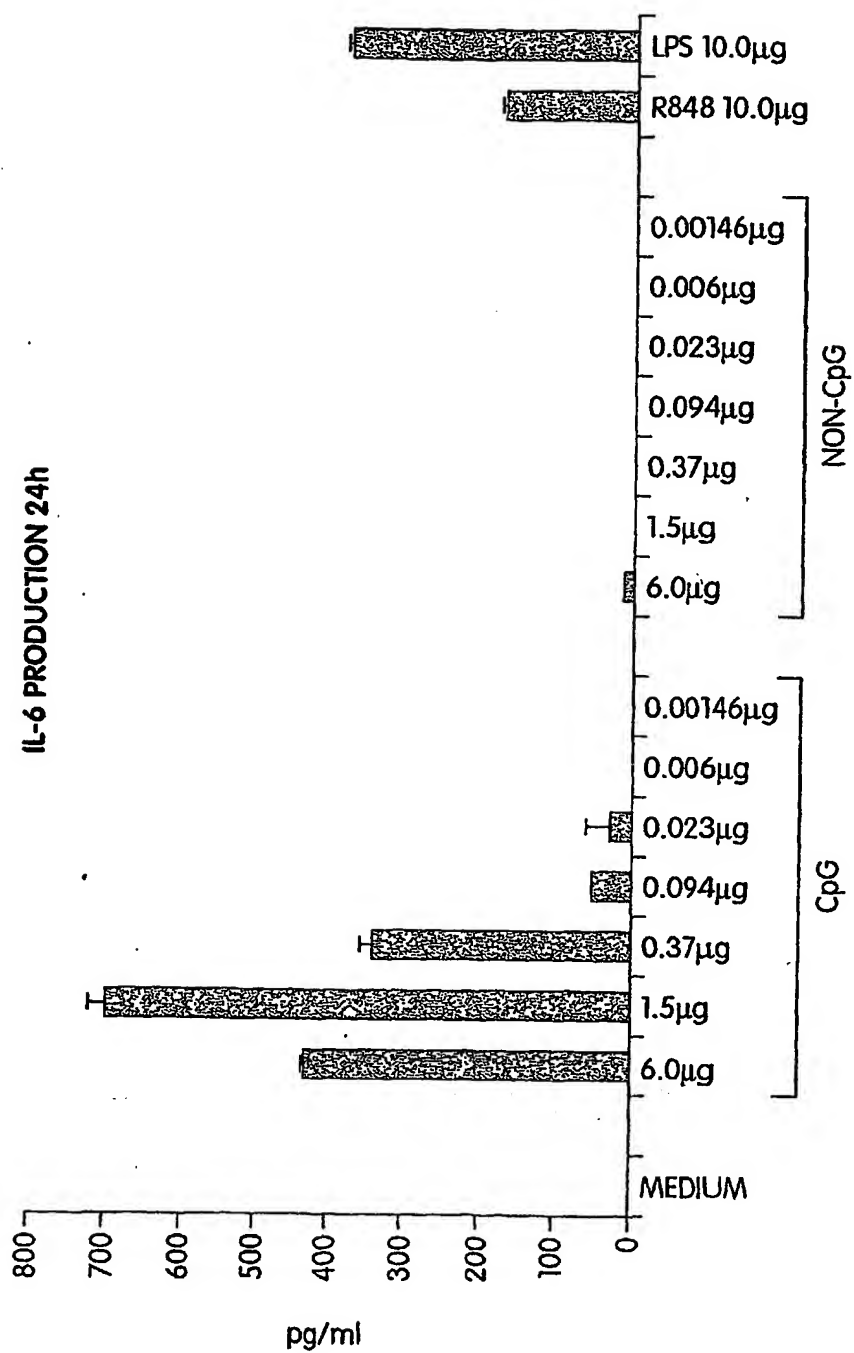


Fig. 3

4/15

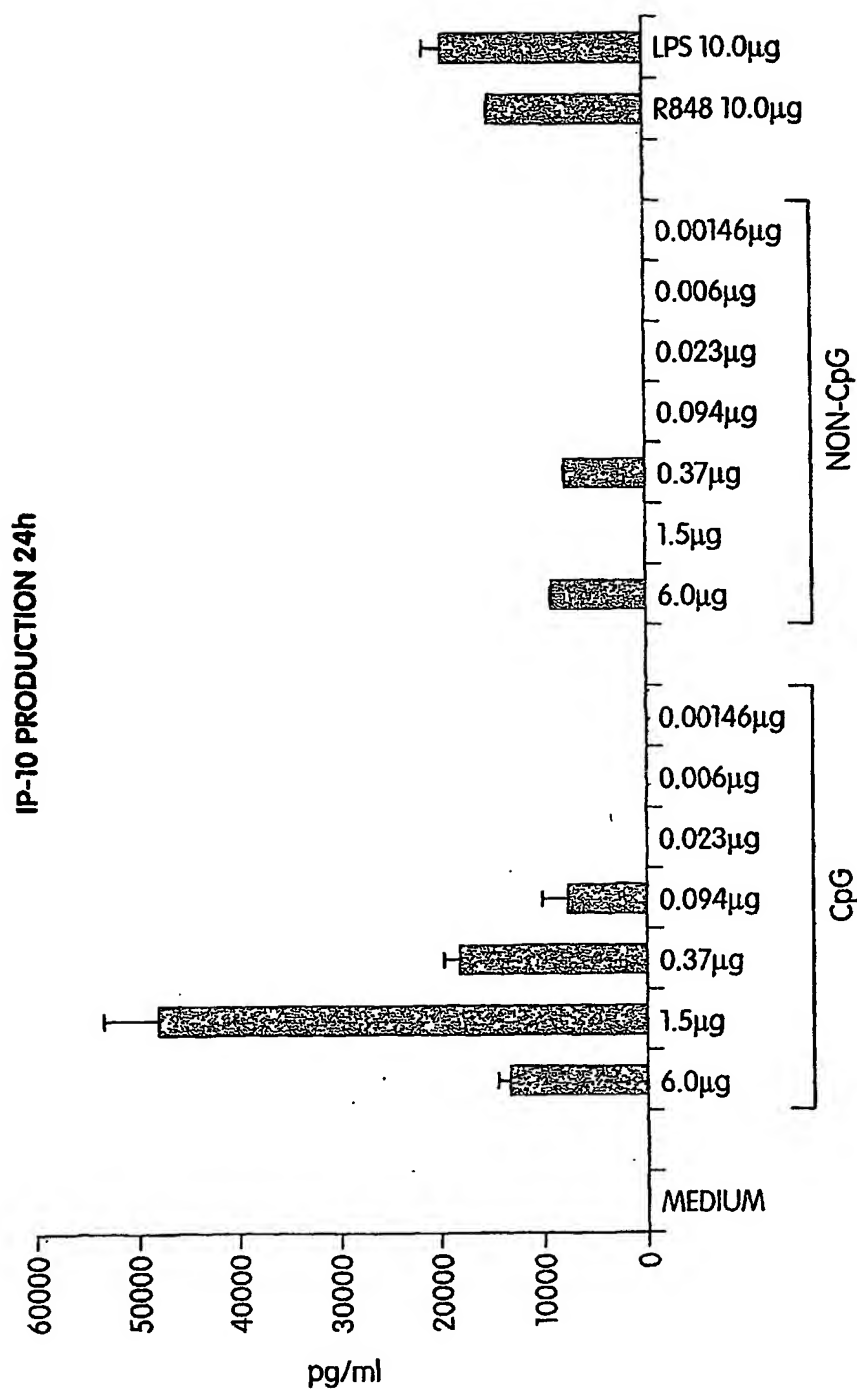


Fig. 4

5/15

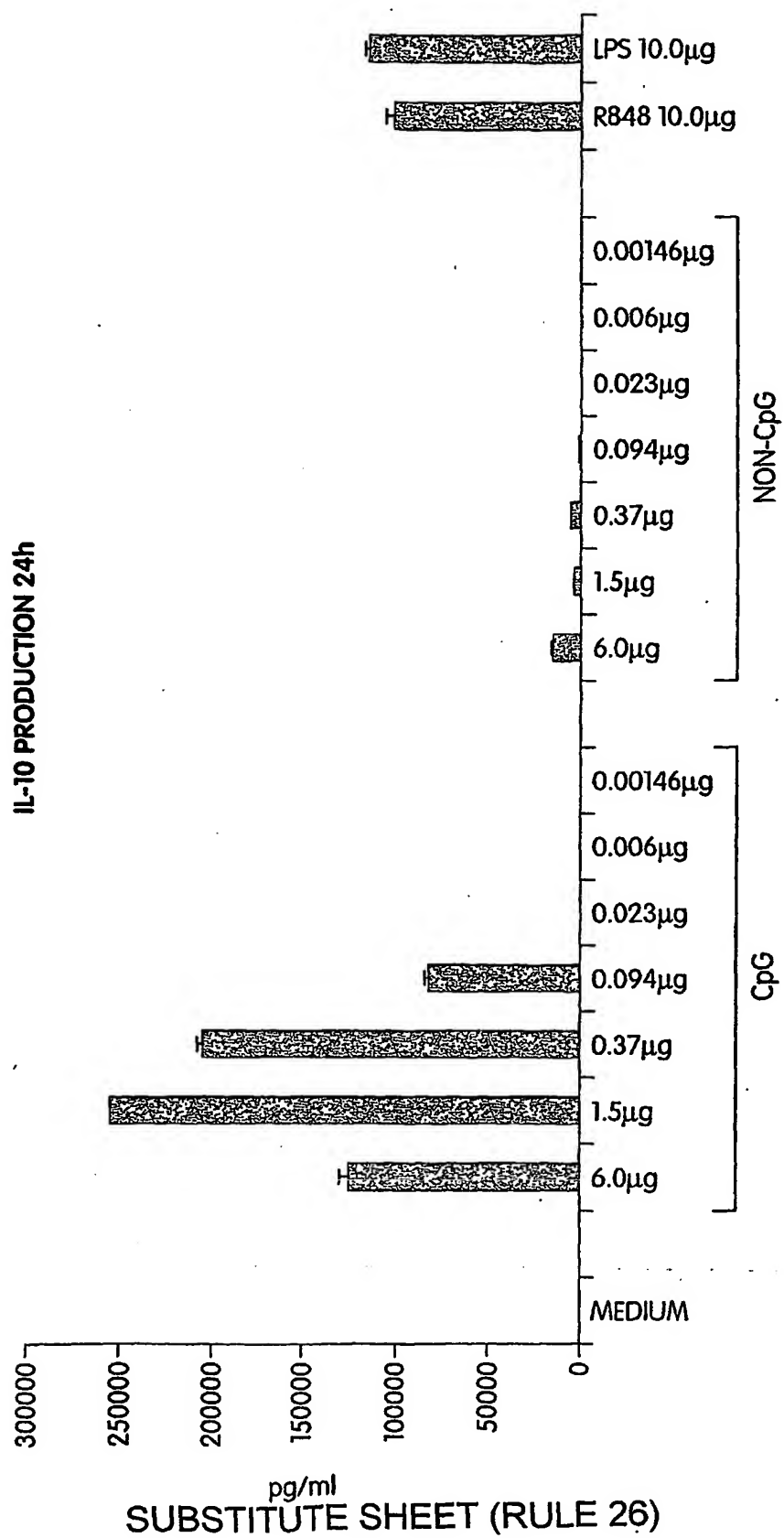


Fig. 5

6/15

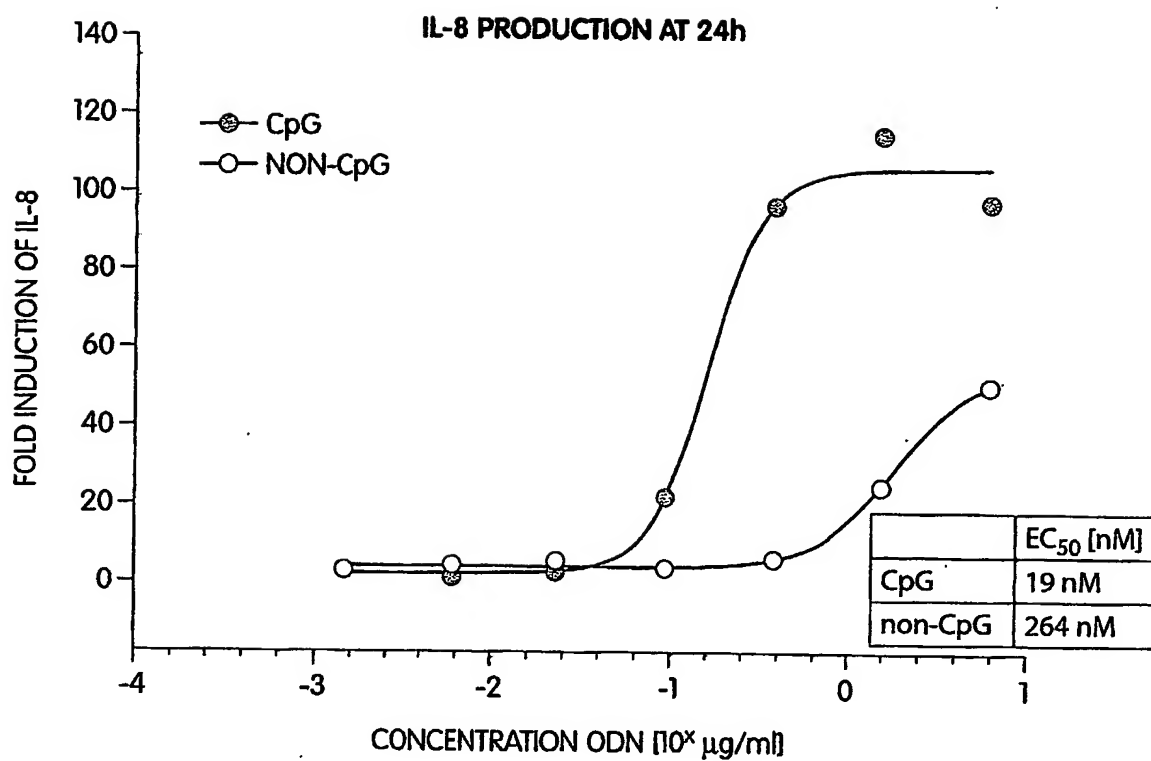


Fig. 6

7/15

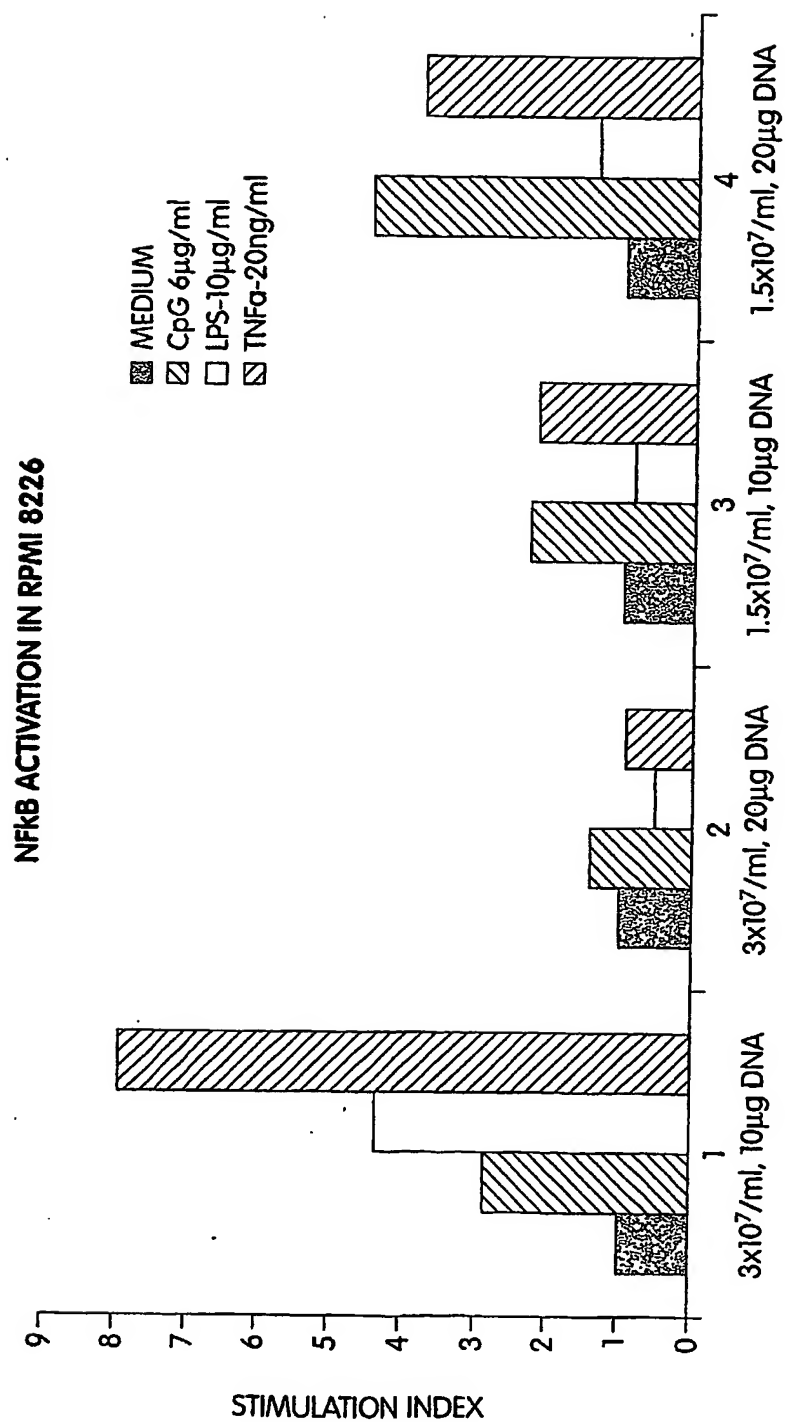


Fig. 7

8/15

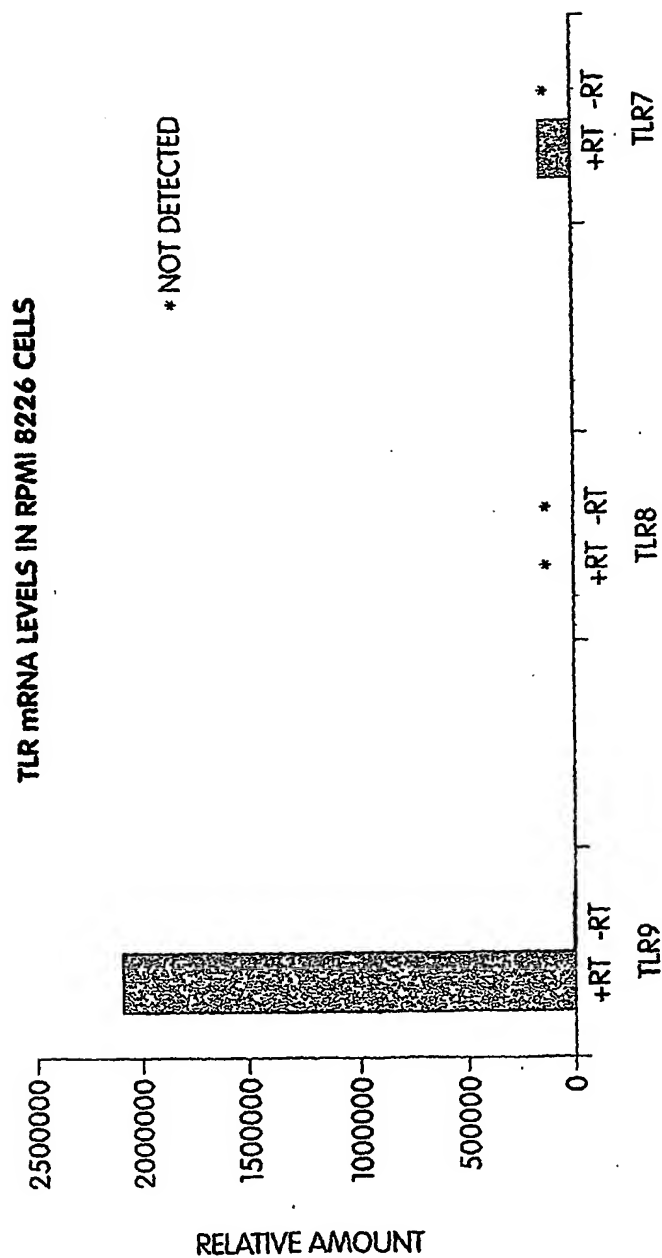


Fig. 8

9/15

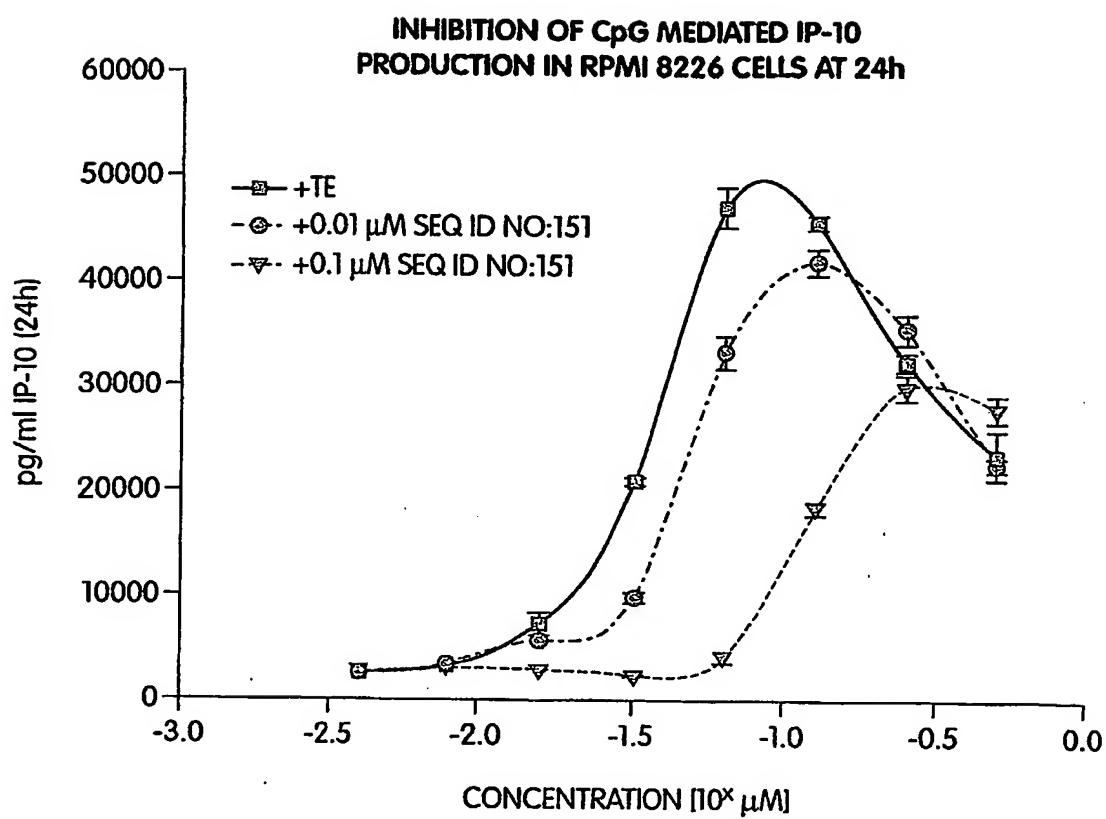


Fig. 9

10/15

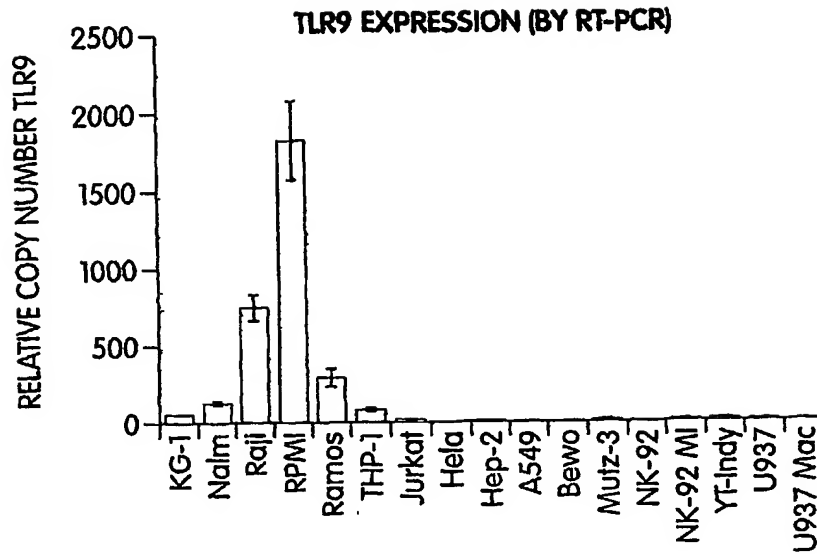


Fig. 10

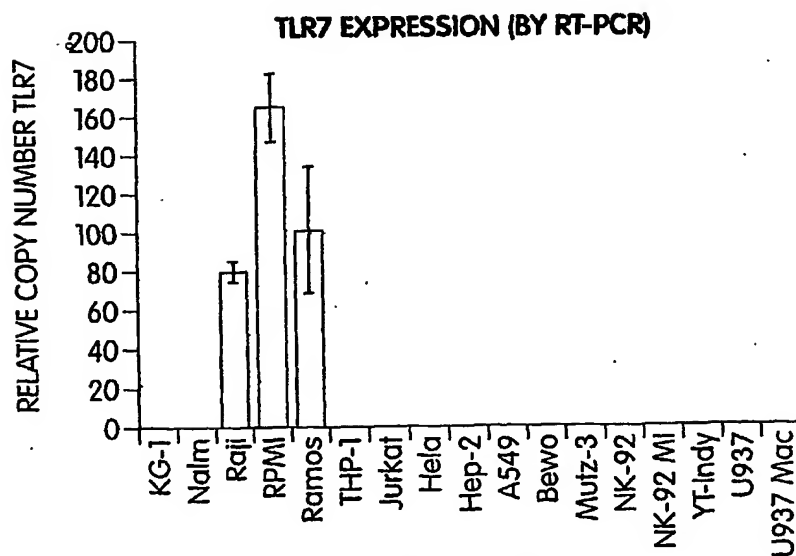


Fig. 11

11/15

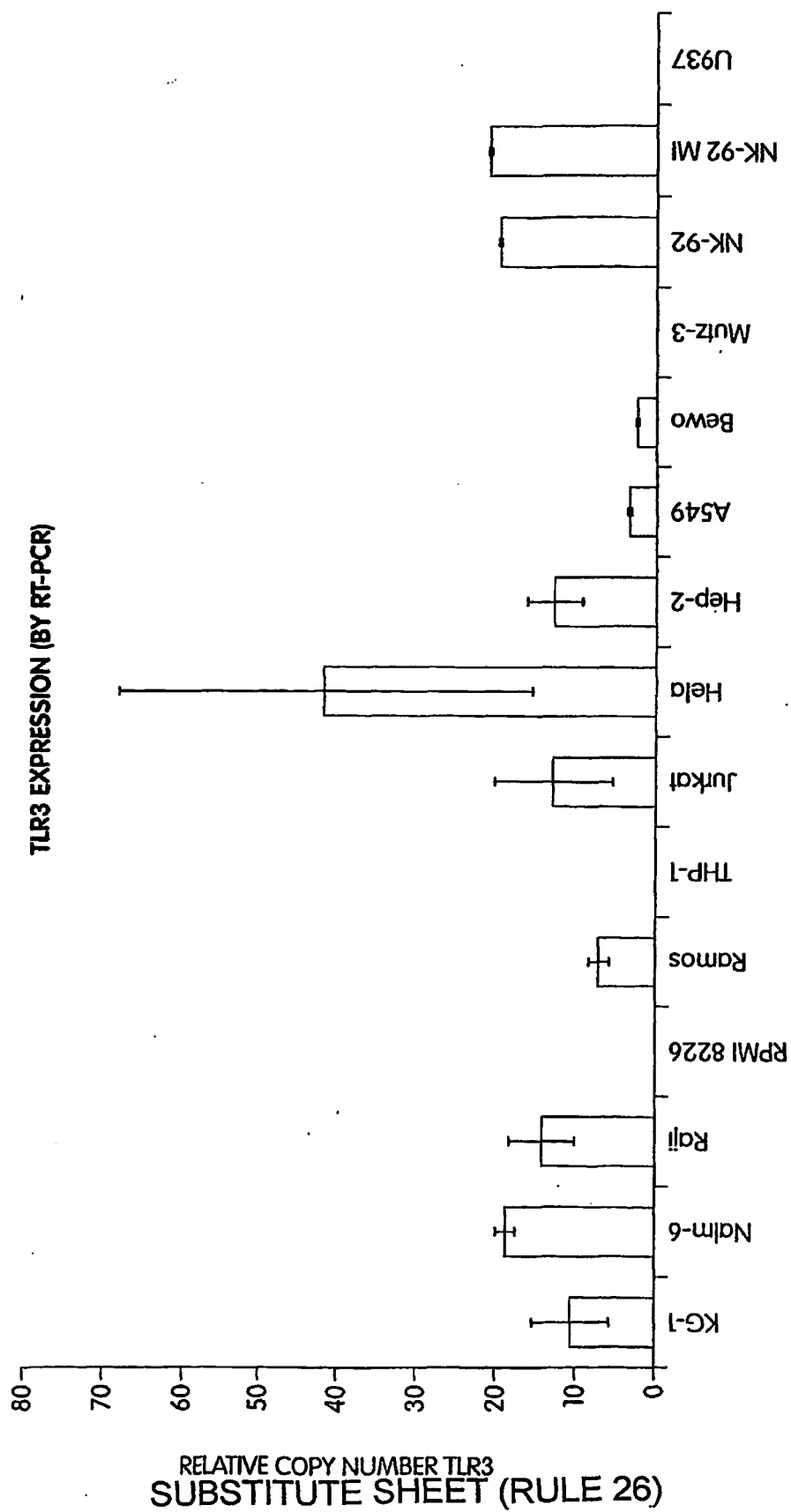


Fig. 12

12/15

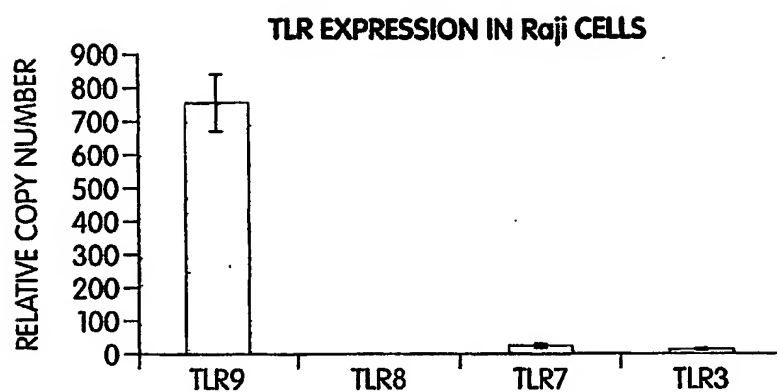


Fig. 13

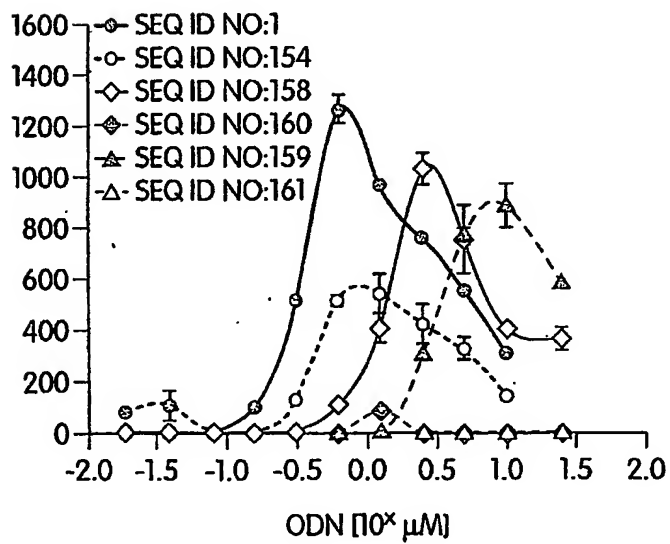


Fig. 14

13/15

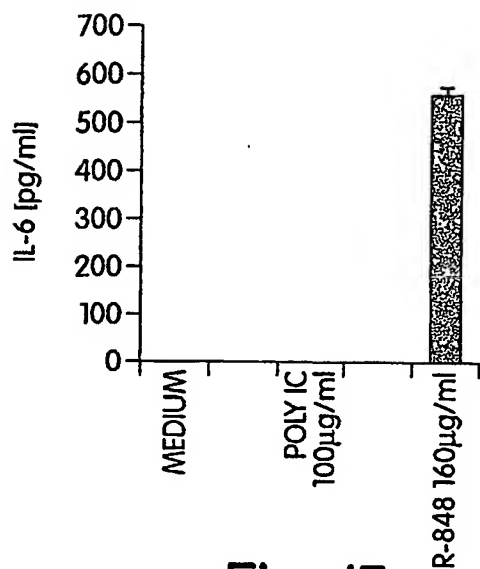


Fig. 15

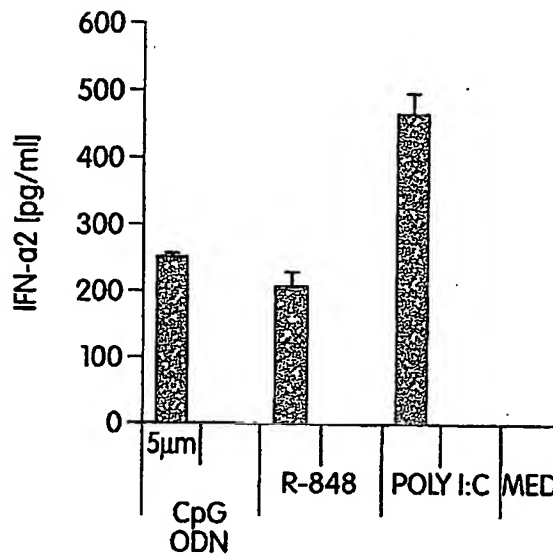


Fig. 16

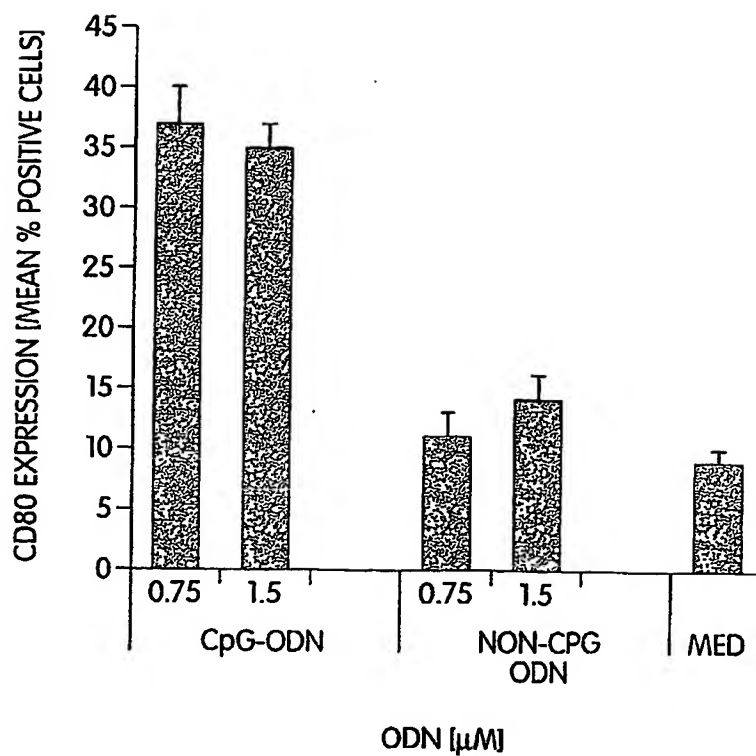


Fig. 17

SUBSTITUTE SHEET (RULE 26)

14/15

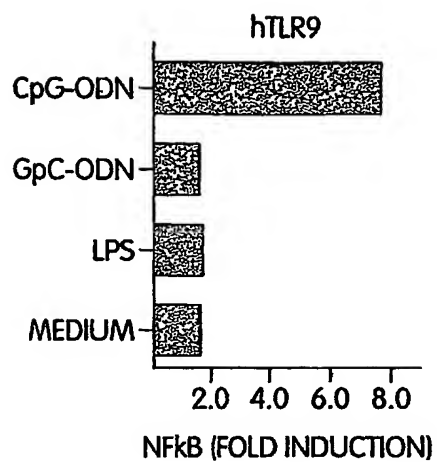


Fig. 18A

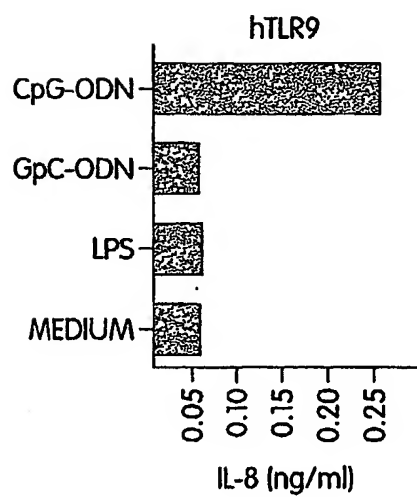


Fig. 18B

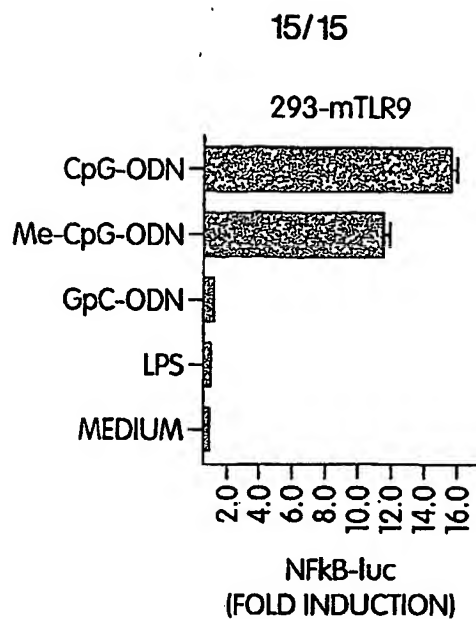


Fig. 19

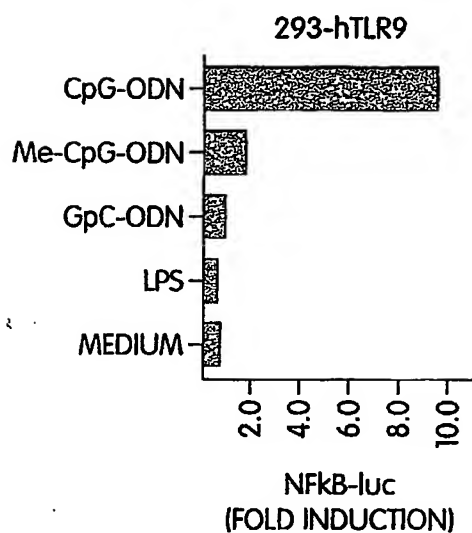
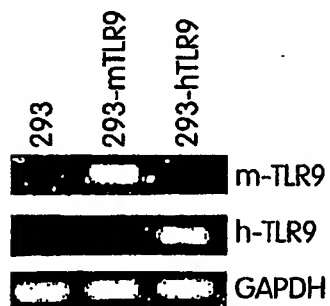


Fig. 20



SEQUENCE LISTING

<110> COLEY PHARMACEUTICAL GmbH
COLEY PHARMACEUTICAL GROUP INC.

<120> METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT OF TLR
LIGANDS

<130> C1041.70024W000

<140> not yet assigned
<141> 2004-04-22

<150> US 60/464,586
<151> 2003-04-22

<150> US 60/464,588
<151> 2003-04-22

<160> 161

<170> PatentIn version 3.2

<210> 1
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> oligonucleotide

<400> 1
tcgctcggtttt gtcgttttgt cggt 24

<210> 2
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> oligonucleotide

<400> 2
tccaggactt ctctcagggt 20

<210> 3
<211> 2600
<212> DNA
<213> Homo sapiens

<400> 3
ggatccaaag gagacctata gtgactccca ggagctctta gtgaccaagt gaaggtaacct 60
gtggggctca ttgtgcccat tgctctttca ctgctttcaa ctggtagttg tgggttgaag 120
cactggacaa tgccacatac tttgtggatg gtgtgggtct tgggggtcat catcagcctc 180
tccaaggaag aatcctccaa tcaggcttct ctgtcttgtg accgcaatgg tatctgcaag 240

ggcagctcag gatcttttaa ctccattccc tcagggctca cagaagctgt aaaaagcctt 300
 gacctgtcca acaacaggat cacctacatt agcaacagtg acctacagag gtgtgtgaac 360
 ctccaggctc tgggtgctgac atccaatgga attaacacaa tagaggaaga ttctttttct 420
 tccttgggca gtcttgaaca tttagactta tcctataatt acttatctaa tttatcgtct 480
 tcctgggtca agccccttct ttctttaaca ttcttaaaact tactgggaaa tccttacaaa 540
 accctagggg aaacatctct tttttctcat ctacacaaaat tgcaaatcct gagagtggga 600
 aatatggaca ccttcactaa gattcaaaga aaagattttg ctggacttac cttccttgag 660
 gaacttgaga ttgatgcttc agatctacag agctatgagc caaaaagttt gaagtcaatt 720
 cagaacgtaa gtcattctgat ccttcattatg aagcagcata ttttactgct ggagattttt 780
 gtagatgtta caagtccgt ggaatgtttg gaactgcgag atactgattt ggacactttc 840
 catttttcag aactatccac tggtgaaaca aattcattga ttaaaaagtt tacatttaga 900
 aatgtgaaaa tcaccgatga aagtttggtt caggttatga aacttttgaa tcagattttct 960
 ggattgttag aattagagtt tgatgactgt acccttaatg gagttggtta ttttagagca 1020
 tctgataatg acagagttat agatccaggt aaagtggaaa cgtaacaat ccggaggctg 1080
 catattccaa ggttttactt attttatgat ctgagcactt tatattcact tacagaaaga 1140
 gttaaaagaa tcacagtaga aaacagtaaa gtttttctgg ttccttggtt actttcacia 1200
 catttaaaat cattagaata cttggatctc agtgaaaatt tgatggttga agaatacttg 1260
 aaaaattcag cctgtgagga tgccctggccc tctctacaaa ctttaatttt aaggcaaat 1320
 catttgcat cattggaaaa aaccggagag actttgctca ctctgaaaaa cttgactaac 1380
 attgatatca gtaagaatag ttttcattct atgcctgaaa cttgtcagtg gccagaaaag 1440
 atgaaatatt tgaacttatc cagcacacga atacacagtg taacaggctg cattcccaag 1500
 aactggaaa ttttagatgt tagcaacaac aatctcaatt tattttcttt gaatttgccg 1560
 caactcaaag aactttatat ttccagaaat aagttgatga ctctaccaga tgcctccctc 1620
 ttacccatgt tactagtatt gaaaatcagt aggaatgcaa taactacgtt ttctaaggag 1680
 caacttgact catttcacac actgaagact ttggaagctg gtggcaataa cttcatttgc 1740
 tcctgtgaat tcctctcctt cactcaggag cagcaagcac tggccaaagt cttgattgat 1800
 tggccagcaa attacctgtg tgactctcca tcccatgtgc gtggccagca ggttcaggat 1860
 gtccgcctct cgggtgcgga atgtcacagg acagcactgg tgtctggcat gtgctgtgct 1920
 ctgttcctgc tgatcctgct cacgggggtc ctgtgccacc gtttccatgg cctgtgggat 1980
 atgaaaatga tgtgggcctg gctccaggcc aaaaggaagc ccaggaaagc tccagcagg 2040
 aacatctgct atgatgcatt tgtttcttac agtgagcggg atgcctactg ggtggagaac 2100

cttatgggtcc aggagctgga gaacttcaat ccccccttca agttgtgtct tcataagcgg 2160
 gacttcattc ctggcaagtg gatcattgac aatatcattg actccattga aaagagccac 2220
 aaaactgtct ttgtgctttc tgaaaacttt gtgaagagtg agtgggtgcaa gtatgaactg 2280
 gacttctccc atttccgtct ttttgaagag aacaatgatg ctgccattct cattcttctg 2340
 gagcccattg agaaaaaagc cattccccag cgcttctgca agctgcggaa gataatgaac 2400
 accaagacct acctggagtg gcccatggac gaggtcagc ggggaaggatt ttgggtaaat 2460
 ctgagagctg cgataaagtc ctaggttccc atatttaaga ccagtctttg tctagttggg 2520
 atctttatgt cactagttat agttaagttc attcagacat aattatataa aaactacgtg 2580
 gatgtaccgt catttgagga 2600

<210> 4
 <211> 784
 <212> PRT
 <213> Homo sapiens

<400> 4

Met Pro His Thr Leu Trp Met Val Trp Val Leu Gly Val Ile Ile Ser
 1 5 10 15
 Leu Ser Lys Glu Glu Ser Ser Asn Gln Ala Ser Leu Ser Cys Asp Arg
 20 25 30
 Asn Gly Ile Cys Lys Gly Ser Ser Gly Ser Leu Asn Ser Ile Pro Ser
 35 40 45
 Gly Leu Thr Glu Ala Val Lys Ser Leu Asp Leu Ser Asn Asn Arg Ile
 50 55 60
 Thr Tyr Ile Ser Asn Ser Asp Leu Gln Arg Cys Val Asn Leu Gln Ala
 65 70 75 80
 Leu Val Leu Thr Ser Asn Gly Ile Asn Thr Ile Glu Glu Asp Ser Phe
 85 90 95
 Ser Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Tyr Asn Tyr Leu
 100 105 110
 Ser Asn Leu Ser Ser Ser Trp Phe Lys Pro Leu Ser Ser Leu Thr Phe
 115 120 125
 Leu Asn Leu Leu Gly Asn Pro Tyr Lys Thr Leu Gly Glu Thr Ser Leu
 130 135 140
 Phe Ser His Leu Thr Lys Leu Gln Ile Leu Arg Val Gly Asn Met Asp
 145 150 155 160
 Thr Phe Thr Lys Ile Gln Arg Lys Asp Phe Ala Gly Leu Thr Phe Leu
 165 170 175
 Glu Glu Leu Glu Ile Asp Ala Ser Asp Leu Gln Ser Tyr Glu Pro Lys
 180 185 190

Ser Leu Lys Ser Ile Gln Asn Val Ser His Leu Ile Leu His Met Lys
 195 200 205
 Gln His Ile Leu Leu Leu Glu Ile Phe Val Asp Val Thr Ser Ser Val
 210 215 220
 Glu Cys Leu Glu Leu Arg Asp Thr Asp Leu Asp Thr Phe His Phe Ser
 225 230 235 240
 Glu Leu Ser Thr Gly Glu Thr Asn Ser Leu Ile Lys Lys Phe Thr Phe
 245 250 255
 Arg Asn Val Lys Ile Thr Asp Glu Ser Leu Phe Gln Val Met Lys Leu
 260 265 270
 Leu Asn Gln Ile Ser Gly Leu Leu Glu Leu Glu Phe Asp Asp Cys Thr
 275 280 285
 Leu Asn Gly Val Gly Asn Phe Arg Ala Ser Asp Asn Asp Arg Val Ile
 290 295 300
 Asp Pro Gly Lys Val Glu Thr Leu Thr Ile Arg Arg Leu His Ile Pro
 305 310 315 320
 Arg Phe Tyr Leu Phe Tyr Asp Leu Ser Thr Leu Tyr Ser Leu Thr Glu
 325 330 335
 Arg Val Lys Arg Ile Thr Val Glu Asn Ser Lys Val Phe Leu Val Pro
 340 345 350
 Cys Leu Leu Ser Gln His Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
 355 360 365
 Glu Asn Leu Met Val Glu Glu Tyr Leu Lys Asn Ser Ala Cys Glu Asp
 370 375 380
 Ala Trp Pro Ser Leu Gln Thr Leu Ile Leu Arg Gln Asn His Leu Ala
 385 390 395 400
 Ser Leu Glu Lys Thr Gly Glu Thr Leu Leu Thr Leu Lys Asn Leu Thr
 405 410 415
 Asn Ile Asp Ile Ser Lys Asn Ser Phe His Ser Met Pro Glu Thr Cys
 420 425 430
 Gln Trp Pro Glu Lys Met Lys Tyr Leu Asn Leu Ser Ser Thr Arg Ile
 435 440 445
 His Ser Val Thr Gly Cys Ile Pro Lys Thr Leu Glu Ile Leu Asp Val
 450 455 460
 Ser Asn Asn Asn Leu Asn Leu Phe Ser Leu Asn Leu Pro Gln Leu Lys
 465 470 475 480
 Glu Leu Tyr Ile Ser Arg Asn Lys Leu Met Thr Leu Pro Asp Ala Ser
 485 490 495
 Leu Leu Pro Met Leu Leu Val Leu Lys Ile Ser Arg Asn Ala Ile Thr
 500 505 510
 Thr Phe Ser Lys Glu Gln Leu Asp Ser Phe His Thr Leu Lys Thr Leu

515 520 525
 Glu Ala Gly Gly Asn Asn Phe Ile Cys Ser Cys Glu Phe Leu Ser Phe
 530 535 540
 Thr Gln Glu Gln Gln Ala Leu Ala Lys Val Leu Ile Asp Trp Pro Ala
 545 550 555 560
 Asn Tyr Leu Cys Asp Ser Pro Ser His Val Arg Gly Gln Gln Val Gln
 565 570 575
 Asp Val Arg Leu Ser Val Ser Glu Cys His Arg Thr Ala Leu Val Ser
 580 585 590
 Gly Met Cys Cys Ala Leu Phe Leu Leu Ile Leu Leu Thr Gly Val Leu
 595 600 605
 Cys His Arg Phe His Gly Leu Trp Tyr Met Lys Met Met Trp Ala Trp
 610 615 620
 Leu Gln Ala Lys Arg Lys Pro Arg Lys Ala Pro Ser Arg Asn Ile Cys
 625 630 635 640
 Tyr Asp Ala Phe Val Ser Tyr Ser Glu Arg Asp Ala Tyr Trp Val Glu
 645 650 655
 Asn Leu Met Val Gln Glu Leu Glu Asn Phe Asn Pro Pro Phe Lys Leu
 660 665 670
 Cys Leu His Lys Arg Asp Phe Ile Pro Gly Lys Trp Ile Ile Asp Asn
 675 680 685
 Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser
 690 695 700
 Glu Asn Phe Val Lys Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser
 705 710 715 720
 His Phe Arg Leu Phe Glu Glu Asn Asn Asp Ala Ala Ile Leu Ile Leu
 725 730 735
 Leu Glu Pro Ile Glu Lys Lys Ala Ile Pro Gln Arg Phe Cys Lys Leu
 740 745 750
 Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Met Asp Glu
 755 760 765
 Ala Gln Arg Glu Gly Phe Trp Val Asn Leu Arg Ala Ala Ile Lys Ser
 770 775 780

<210> 5

<211> 2824

<212> DNA

<213> murine

<400> 5

gccccccatg gccatatggg caccgggggag cggcgggctgg aggactccta ggctcctggg 60

caggcgggtca catggcagaa gatgtgtccg caatcatagt ttctgatggt gaaggttggg 120

cggcagtcctc tgcgacctag aagtggaaaa gatgtcgttc aaggaggtgc ggactgtttc 180

cttctgacca	ggatccttgtt	tctgagtgt	ggggcttcac	ttctctgctt	ttcgttcac	240
tctggagcat	ccgaattgca	tcaccggtca	gaaaacaact	taccgaaacc	tcagacaaag	300
cgtcaaattct	cagaggatgc	tacgagctct	ttggctcttc	tggatcttgg	tggccataac	360
agtctctctc	agcaaacgct	gttctggtca	ggagtctctg	tcatgtgatg	cttctggggg	420
gtgtgatggc	cgtccagggt	ctttcacctc	tattccctcc	ggactcacag	cagccatgaa	480
aagccttgac	ctgtctttca	acaagatcac	ctacattggc	catggtgacc	tccgagcgtg	540
tgcgaacctc	caggtttctga	ttttgaagtc	cagcagaatc	aatacaatag	agggagacgc	600
cttttattct	ctgggcagtc	ttgaacattt	ggatttgtct	gataatcacc	tatctagttt	660
atcttctctc	tgggtcgggc	ccctttcctc	tttgaaatac	ttaaacttaa	tgggaaatcc	720
ttaccagaca	ctggggggtaa	catcgctttt	tcccaatctc	acaaatttac	aaaccctcag	780
gataggaaat	gtagagactt	tcagtggat	aaggagaata	gattttgctg	ggctgacttc	840
tctcaatgaa	cttgaaatta	aggcattaag	tctccggaat	tatcagtcct	aaagtctaaa	900
gtcgatccgc	gacatccatc	acctgactct	tcacttaagc	gagtctgctt	tcctgctgga	960
gatttttgca	gatattctga	gttctgtgag	atatttagaa	ctaagagata	ctaacttggc	1020
caggttccag	ttttcaccac	tgcccgtaga	tgaagtcagc	tcaccgatga	agaagctggc	1080
attccgaggc	tcggtttctca	ctgatgaaag	ctttaacgag	ctcctgaagc	tgttgcggtta	1140
catcttgcaa	ctgtcggagg	tagagtctga	cgactgtacc	ctcaatgggc	tcggcgattt	1200
caaccctcgc	gagtcagacg	tagtgagcga	gctgggtaaa	gtagaaacag	tcactatccg	1260
gaggttgcat	atccccagct	tctatttgtt	ttatgacctg	agtactgtct	attccctcct	1320
ggagaagggtg	aagcgaatca	cagtagagaa	cagcaagggtc	ttcctgggtc	cctgctcggt	1380
ctcccagcat	ttaaaatcat	tagaattctt	agacctcagc	gaaaatctga	tgggtgaaga	1440
atatttgaa	aactcagcct	gtaaggagc	ctggccttct	ctacaaacct	tagttttgag	1500
ccagaatcat	ttgagatcaa	tgcaaaaaac	aggagagatt	ttgctgactc	tgaaaaacct	1560
gacctccctt	gacatcagca	ggaacacttt	tcattccgatg	cccgacagct	gtcagtggcc	1620
agaaaagatg	cgcttctctga	atttgtccag	tacagggatc	cgggtggtaa	aaacgtgcat	1680
tcctcagacg	ctggagggtg	tggatgttag	taacaacaat	cttgactcat	tttctttgtt	1740
cttgctcggg	ctgcaagagc	tctatatttc	cagaaataag	ctgaaaacac	tcccagatgc	1800
ttcgttgttc	cctgtgttgc	tggatcatgaa	aatcagagag	aatgcagtaa	gtactttctc	1860
taaagaccaa	cttgggttctt	ttcccaaact	ggagactctg	gaagcaggcg	acaaccactt	1920
tgtttgctcc	tgcaaacctc	tatcctttac	tatggagacg	ccagctctgg	ctcaaatcct	1980
ggttgactgg	ccagacagct	acctgtgtga	ctctccgcct	cgctgcacg	gccacaggct	2040
tcaggatgcc	cggccctccg	tcttggaatg	tcaccaggct	gcactgggtg	ctggagtctg	2100

```

ctgtgccctt ctcctgttga tcttgctcgt aggtgccctg tgccaccatt tccacgggct 2160
gtggtagctg agaatgatgt gggcgtaggt ccaggccaag aggaagccca agaaagctcc 2220
ctgcagggac gtttgctatg atgcctttgt ttcctacagt gagcaggatt cccattgggt 2280
ggagaacctc atggtccagc agctggagaa ctctgacctg ccctttaagc tgtgtctcca 2340
caagcgggac ttcgttccgg gcaaattgat cattgacaac atcatcgatt ccatcgaaaa 2400
gagccacaaa actgtgttcg tgctttctga gaacttcgta cggagcgagt ggtgcaagta 2460
cgaactggac ttctccact tcaggctctt tgacgagaac aacgacgcgg ccatccttgt 2520
tttgctggag cccattgaga ggaaagccat tccccagcgc ttctgcaaac tgcgcaagat 2580
aatgaacacc aagacctacc tggagtggcc cttggatgaa ggccagcagg aagtgttttg 2640
ggtaaactctg agaactgcaa taaagtcta ggttctccac ccagttcctg acttccttaa 2700
ctaaggctctt tgtgacacaa actgtaacaa agtttataag taacatagaa ttgtattatt 2760
gaggatatta actatgggtt ttgtcttgaa tactgttata taaatatgtg acatcaggct 2820
ttag 2824

```

<210> 6
 <211> 784
 <212> PRT
 <213> murine

<400> 6

```

Met Leu Arg Ala Leu Trp Leu Phe Trp Ile Leu Val Ala Ile Thr Val
1           5           10          15

Leu Phe Ser Lys Arg Cys Ser Ala Gln Glu Ser Leu Ser Cys Asp Ala
20          25          30

Ser Gly Val Cys Asp Gly Arg Ser Arg Ser Phe Thr Ser Ile Pro Ser
35          40          45

Gly Leu Thr Ala Ala Met Lys Ser Leu Asp Leu Ser Phe Asn Lys Ile
50          55          60

Thr Tyr Ile Gly His Gly Asp Leu Arg Ala Cys Ala Asn Leu Gln Val
65          70          75          80

Leu Ile Leu Lys Ser Ser Arg Ile Asn Thr Ile Glu Gly Asp Ala Phe
85          90          95

Tyr Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Asp Asn His Leu
100         105         110

Ser Ser Leu Ser Ser Ser Trp Phe Gly Pro Leu Ser Ser Leu Lys Tyr
115         120         125

Leu Asn Leu Met Gly Asn Pro Tyr Gln Thr Leu Gly Val Thr Ser Leu
130         135         140

```

Phe Pro Asn Leu Thr Asn Leu Gln Thr Leu Arg Ile Gly Asn Val Glu
 145 150 155 160
 Thr Phe Ser Glu Ile Arg Arg Ile Asp Phe Ala Gly Leu Thr Ser Leu
 165 170 175
 Asn Glu Leu Glu Ile Lys Ala Leu Ser Leu Arg Asn Tyr Gln Ser Gln
 180 185 190
 Ser Leu Lys Ser Ile Arg Asp Ile His His Leu Thr Leu His Leu Ser
 195 200 205
 Glu Ser Ala Phe Leu Leu Glu Ile Phe Ala Asp Ile Leu Ser Ser Val
 210 215 220
 Arg Tyr Leu Glu Leu Arg Asp Thr Asn Leu Ala Arg Phe Gln Phe Ser
 225 230 235 240
 Pro Leu Pro Val Asp Glu Val Ser Ser Pro Met Lys Lys Leu Ala Phe
 245 250 255
 Arg Gly Ser Val Leu Thr Asp Glu Ser Phe Asn Glu Leu Leu Lys Leu
 260 265 270
 Leu Arg Tyr Ile Leu Glu Leu Ser Glu Val Glu Phe Asp Asp Cys Thr
 275 280 285
 Leu Asn Gly Leu Gly Asp Phe Asn Pro Ser Glu Ser Asp Val Val Ser
 290 295 300
 Glu Leu Gly Lys Val Glu Thr Val Thr Ile Arg Arg Leu His Ile Pro
 305 310 315 320
 Gln Phe Tyr Leu Phe Tyr Asp Leu Ser Thr Val Tyr Ser Leu Leu Glu
 325 330 335
 Lys Val Lys Arg Ile Thr Val Glu Asn Ser Lys Val Phe Leu Val Pro
 340 345 350
 Cys Ser Phe Ser Gln His Leu Lys Ser Leu Glu Phe Leu Asp Leu Ser
 355 360 365
 Glu Asn Leu Met Val Glu Glu Tyr Leu Lys Asn Ser Ala Cys Lys Gly
 370 375 380
 Ala Trp Pro Ser Leu Gln Thr Leu Val Leu Ser Gln Asn His Leu Arg
 385 390 395 400
 Ser Met Gln Lys Thr Gly Glu Ile Leu Leu Thr Leu Lys Asn Leu Thr
 405 410 415
 Ser Leu Asp Ile Ser Arg Asn Thr Phe His Pro Met Pro Asp Ser Cys
 420 425 430
 Gln Trp Pro Glu Lys Met Arg Phe Leu Asn Leu Ser Ser Thr Gly Ile
 435 440 445
 Arg Val Val Lys Thr Cys Ile Pro Gln Thr Leu Glu Val Leu Asp Val
 450 455 460
 Ser Asn Asn Asn Leu Asp Ser Phe Ser Leu Phe Leu Pro Arg Leu Gln

465 470 475 480
 Glu Leu Tyr Ile Ser Arg Asn Lys Leu Lys Thr Leu Pro Asp Ala Ser
 485 490 495

 Leu Phe Pro Val Leu Leu Val Met Lys Ile Arg Glu Asn Ala Val Ser
 500 505 510

 Thr Phe Ser Lys Asp Gln Leu Gly Ser Phe Pro Lys Leu Glu Thr Leu
 515 520 525

 Glu Ala Gly Asp Asn His Phe Val Cys Ser Cys Glu Leu Leu Ser Phe
 530 535 540

 Thr Met Glu Thr Pro Ala Leu Ala Gln Ile Leu Val Asp Trp Pro Asp
 545 550 555 560

 Ser Tyr Leu Cys Asp Ser Pro Pro Arg Leu His Gly His Arg Leu Gln
 565 570 575

 Asp Ala Arg Pro Ser Val Leu Glu Cys His Gln Ala Ala Leu Val Ser
 580 585 590

 Gly Val Cys Cys Ala Leu Leu Leu Leu Ile Leu Leu Val Gly Ala Leu
 595 600 605

 Cys His His Phe His Gly Leu Trp Tyr Leu Arg Met Met Trp Ala Trp
 610 615 620

 Leu Gln Ala Lys Arg Lys Pro Lys Lys Ala Pro Cys Arg Asp Val Cys
 625 630 635 640

 Tyr Asp Ala Phe Val Ser Tyr Ser Glu Gln Asp Ser His Trp Val Glu
 645 650 655

 Asn Leu Met Val Gln Gln Leu Glu Asn Ser Asp Pro Pro Phe Lys Leu
 660 665 670

 Cys Leu His Lys Arg Asp Phe Val Pro Gly Lys Trp Ile Ile Asp Asn
 675 680 685

 Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser
 690 695 700

 Glu Asn Phe Val Arg Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser
 705 710 715 720

 His Phe Arg Leu Phe Asp Glu Asn Asn Asp Ala Ala Ile Leu Val Leu
 725 730 735

 Leu Glu Pro Ile Glu Arg Lys Ala Ile Pro Gln Arg Phe Cys Lys Leu
 740 745 750

 Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Leu Asp Glu
 755 760 765

 Gly Gln Gln Glu Val Phe Trp Val Asn Leu Arg Thr Ala Ile Lys Ser
 770 775 780

<210> 7
 <211> 3029
 <212> DNA

<213> Homo sapiens

<400> 7

```

gcggccgcgt cgacgaaatg tctggatttg gactaaagaa aaaaggaaag gctagcagtc      60
atccaacaga atcatgagac agactttgcc ttgtatctac ttttgggggg gccttttgcc      120
ctttgggatg ctgtgtgcat cctccaccac caagtgcact gttagccatg aagttgctga      180
ctgcagccac ctgaagttga ctcaggtacc cgatgatcta cccacaaaca taacagtgtt      240
gaaccttacc cataatcaac tcagaagatt accagccgcc aacttcacaa ggtatagcca      300
gctaactagc ttggatgtag gatttaacac catctcaaaa ctggagccag aattgtgcca      360
gaaacttccc atgttaaaag ttttgaacct ccagcacaat gagctatctc aactttctga      420
taaaaccttt gccttctgca cgaatttgac tgaactccat ctcatgtcca actcaatcca      480
gaaaattaaa aataatccct ttgtcaagca gaagaattta atcacattag atctgtctca      540
taatggcttg tcatctacaa aattaggaac tcagggtcag ctggaaaatc tccaagagct      600
tctattatca aacaataaaa ttcaagcgt aaaaagtga gaactggata tctttgccaa      660
ttcatcttta aaaaaattag agttgtcatc gaatcaaatt aaagagtttt ctccagggtg      720
ttttcacgca attggaagat tatttggcct ctttctgaac aatgtccagc tgggtccag      780
ccttacagag aagctatgtt tggaattagc aaacacaagc attcggaatc tgtctctgag      840
taacagccag ctgtccacca ccagcaatac aactttcttg ggactaaagt ggacaaatct      900
cactatgctc gatctttcct acaacaactt aaatgtggtt ggtaacgatt cctttgcttg      960
gcttcacaaa ctagaatatt tcttcctaga gtataataat atacagcatt tgttttctca     1020
ctctttgcac gggcttttca atgtgaggtt cctgaatttg aaacggtctt ttactaaaca     1080
aagtatttcc cttgcctcac tccccagat tgatgatttt tcttttcagt ggctaaaatg     1140
tttggagcac cttaacatgg aagataatga tattccaggc ataaaaagca atatgttcac     1200
aggattgata aacctgaaat acttaagtct atccaactcc tttacaagtt tgcgaaacttt     1260
gacaaatgaa acatttgat cacttgctca ttctccctta cacatactca acctaaccaa     1320
gaataaaatc tcaaaaatag agegtgatgc tttctcttgg ttgggccacc tagaagtact     1380
tgacctgggc cttaatgaaa ttgggcaaga actcacaggc caggaatgga gaggtctaga     1440
aaatattttc gaaatctatc tttcctacaa caagtacctg cagctgacta ggaactcctt     1500
tgcttgggtc ccaagccttc aacgactgat gctccgaagg gtggccctta aaaatgtgga     1560
tagctctcct tcaccattcc agcctcttcg taacttgacc attctggatc taagcaacaa     1620
caacatagcc aacataaatg atgacatgtt ggagggtctt gagaaactag aaattctcga     1680
tttgcagcat aacaacttag cacggctctg gaaacacgca aaccctggtg gtcccattta     1740
tttcctaaag ggtctgtctc acctccacat ccttaacttg gagtccaacg gctttgacga     1800

```

```

gatcccagtt gaggtcttca aggatttatt tgaactaaag atcatcgatt taggattgaa 1860
taattttaaac acacttccag catctgtctt taataatcag gtgtctctaa agtcattgaa 1920

ccttcagaag aatctcataa catccgttga gaagaagggt ttcgggccag ctttcaggaa 1980

cctgactgag ttagatatgc gctttaatcc ctttgattgc acgtgtgaaa gtattgcctg 2040

gtttgttaat tggattaacg agaccatac caacatccct gagctgtcaa gccactacct 2100

ttgcaacact ccacctcaat atcatggggt cccagtgaga ctttttgata catcatcttg 2160

caaagacagt gcccccttg aactcttttt catgatcaat accagtatcc tgttgatttt 2220

tatctttatt gtactttctca tccactttga gggctggagg atatcttttt attggaatgt 2280

ttcagtacat cgagttcttg gtttcaaaga aatagacaga cagacagaac agtttgaata 2340

tgcagcatat ataattcatg cctataaaga taaggattgg gtctgggaac atttctcttc 2400

aatggaaaag gaagaccaat ctctcaaatt ttgtctggaa gaaagggact ttgaggcggg 2460

tgtttttgaa ctagaagcaa ttgttaacag catcaaaaga agcagaaaaa ttatttttgt 2520

tataacacac catctattaa aagaccatt atgcaaaaga ttcaaggtag atcatgcagt 2580

tcaacaagct attgaacaaa atctggattc cattatattg gttttccttg aggagattcc 2640

agattataaa ctgaaccatg cactctgttt gcgaagagga atgtttaaat ctcactgcat 2700

cttgaactgg ccagttcaga aagaacggat aggtgccttt cgtcataaat tgcaagtagc 2760

acttgatcc aaaaactctg tacattaaat ttatttaaatt attcaattag caaaggagaa 2820

actttctcaa tttaaaaagt tctatggcaa atttaagttt tccataaagg tgttataatt 2880

tgtttattca tatttgtaaa tgattatatt ctatcacaat tacatctctt ctaggaaaat 2940

gtgtctcctt atttcaggcc tatttttgac aattgactta attttaccba aaataaaaca 3000

tataagcacg caaaaaaaaa aaaaaaaaaa 3029

```

<210> 8

<211> 904

<212> PRT

<213> Homo sapiens

<400> 8

```

Met Arg Gln Thr Leu Pro Cys Ile Tyr Phe Trp Gly Gly Leu Leu Pro
1           5           10           15

```

```

Phe Gly Met Leu Cys Ala Ser Ser Thr Thr Lys Cys Thr Val Ser His
20           25           30

```

```

Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp
35           40           45

```

```

Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg
50           55           60

```

```

Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu

```

65	Asp	Val	Gly	Phe	Asn 85	Thr	Ile	Ser	Lys	Leu 90	Glu	Pro	Glu	Leu	Cys 95	Gln	80
Lys	Leu	Pro	Met 100	Leu	Lys	Val	Leu	Asn 105	Leu	Gln	His	Asn	Glu	Leu	Ser		
Gln	Leu	Ser 115	Asp	Lys	Thr	Phe	Ala 120	Phe	Cys	Thr	Asn	Leu 125	Thr	Glu	Leu		
His	Leu 130	Met	Ser	Asn	Ser	Ile 135	Gln	Lys	Ile	Lys	Asn 140	Asn	Pro	Phe	Val		
Lys 145	Gln	Lys	Asn	Leu	Ile 150	Thr	Leu	Asp	Leu	Ser 155	His	Asn	Gly	Leu	Ser 160		
Ser	Thr	Lys	Leu	Gly 165	Thr	Gln	Val	Gln	Leu 170	Glu	Asn	Leu	Gln	Glu	Leu		
Leu	Leu	Ser 180	Asn	Asn	Lys	Ile	Gln 185	Ala	Leu	Lys	Ser	Glu 190	Glu	Leu	Asp		
Ile	Phe 195	Ala	Asn	Ser	Ser	Leu	Lys 200	Lys	Leu	Glu	Leu	Ser 205	Ser	Asn	Gln		
Ile 210	Lys	Glu	Phe	Ser	Pro	Gly 215	Cys	Phe	His	Ala 220	Ile	Gly	Arg	Leu	Phe		
Gly 225	Leu	Phe	Leu	Asn	Asn 230	Val	Gln	Leu	Gly	Pro 235	Ser	Leu	Thr	Glu	Lys 240		
Leu	Cys	Leu	Glu	Leu 245	Ala	Asn	Thr	Ser	Ile 250	Arg	Asn	Leu	Ser	Leu	Ser		
Asn	Ser	Gln 260	Leu	Ser	Thr	Thr	Ser	Asn 265	Thr	Thr	Phe	Leu 270	Gly	Leu	Lys		
Trp	Thr	Asn 275	Leu	Thr	Met	Leu	Asp 280	Leu	Ser	Tyr	Asn 285	Asn	Leu	Asn	Val		
Val 290	Gly	Asn	Asp	Ser	Phe	Ala 295	Trp	Leu	Pro	Gln 300	Leu	Glu	Tyr	Phe	Phe		
Leu 305	Glu	Tyr	Asn	Asn	Ile 310	Gln	His	Leu	Phe	Ser 315	His	Ser	Leu	His	Gly 320		
Leu	Phe	Asn	Val	Arg 325	Tyr	Leu	Asn	Leu	Lys 330	Arg	Ser	Phe	Thr	Lys	Gln 335		
Ser	Ile	Ser 340	Leu	Ala	Ser	Leu	Pro	Lys 345	Ile	Asp	Asp	Phe	Ser	Phe	Gln		
Trp	Leu 355	Lys	Cys	Leu	Glu	His 360	Leu	Asn	Met	Glu	Asp 365	Asn	Asp	Ile	Pro		
Gly 370	Ile	Lys	Ser	Asn	Met	Phe 375	Thr	Gly	Leu	Ile	Asn 380	Leu	Lys	Tyr	Leu		
Ser 385	Leu	Ser	Asn	Ser	Phe 390	Thr	Ser	Leu	Arg	Thr 395	Leu	Thr	Asn	Glu	Thr 400		
Phe	Val	Ser	Leu	Ala	His	Ser	Pro	Leu	His	Ile	Leu	Asn	Leu	Thr	Lys		

405 410 415
 Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His
 420 425 430
 Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr
 435 440 445
 Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser
 450 455 460
 Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro
 465 470 475 480
 Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp
 485 490 495
 Ser Ser Pro Ser Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp
 500 505 510
 Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly
 515 520 525
 Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg
 530 535 540
 Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly
 545 550 555 560
 Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu
 565 570 575
 Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp
 580 585 590
 Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn
 595 600 605
 Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser
 610 615 620
 Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu
 625 630 635 640
 Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp
 645 650 655
 Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser
 660 665 670
 Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val
 675 680 685
 Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu
 690 695 700
 Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val
 705 710 715 720
 Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val
 725 730 735
 Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu

740 745 750
 Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp
 755 760 765
 Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu
 770 775 780
 Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu
 785 790 795 800
 Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
 805 810 815
 Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
 820 825 830
 His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile
 835 840 845
 Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
 850 855 860
 Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
 865 870 875 880
 Val Gln Lys Glu Arg Ile Gly Ala Phe Arg His Lys Leu Gln Val Ala
 885 890 895
 Leu Gly Ser Lys Asn Ser Val His
 900

<210> 9
 <211> 3310
 <212> DNA
 <213> murine

<400> 9
 tagaatatga tacagggatt gcacccataa tctgggctga atcatgaaag ggtgttcctc 60
 ttatctaattg tactcctttg ggggactttt gtccctatgg attcttcttg tgtcttccac 120
 aaaccaatgc actgtgagat acaacgtagc tgactgcagc catttgaagc taacacacat 180
 acctgatgat cttccctcta acataacagt gttgaatctt actcacaacc aactcagaag 240
 attaccacct accaacttta caagatacag ccaacttgct atcttggatg caggatttaa 300
 ctccatttca aaactggagc cagaactgtg ccaaatactc cttttgttga aagtattgaa 360
 cctgcaacat aatgagctct ctcagatttc tgatcaaacc tttgtcttct gcacgaacct 420
 gacagaactc gatctaattgt ctaactcaat acacaaaatt aaaagcaacc ctttcaaaaa 480
 ccagaagaat ctaatcaaat tagatttgtc tcataatggg ttatcatcta caaagttggg 540
 aacgggggtc caactggaga acctccaaga actgctctta gcaaaaaata aaatccttgc 600
 gttgcgaagt gaagaacttg agtttcttgg caattcttct ttacgaaagt tggacttgct 660
 atcaaatcca cttaaagagt tctccccggg gtgtttccag acaattggca agttattcgc 720

cctcctcttg	aacaacgccc	aactgaaccc	ccacctcaca	gagaagcttt	gctgggaact	780
ttcaaacaca	agcatccaga	atctctctct	ggctaacaac	cagctgctgg	ccaccagcga	840
gagcactttc	tctgggctga	agtggacaaa	tctcaccag	ctcgatcttt	cctacaacaa	900
cctccatgat	gtcggcaacg	gttctctctc	ctatctccca	agcctgaggt	atctgtctct	960
ggagtacaac	aatatacagc	gtctgtcccc	tcgctctttt	tatggactct	ccaacctgag	1020
gtacctgagt	ttgaagcgag	catttactaa	gcaaagtgtt	tcacttgctt	cacatcccaa	1080
cattgacgat	ttttcctttc	aatggttaaa	atatttgga	tatctcaaca	tggatgacaa	1140
taatattcca	agtacaaaa	gcaatacctt	cacgggattg	gtgagtctga	agtacctaag	1200
tctttccaaa	actttcacia	gtttgcaaac	tttaacaaat	gaaacatttg	tgtcacttgc	1260
tcattctccc	ttgctcactc	tcaacttaac	gaaaaatcac	atctcaaaaa	tagcaaatgg	1320
tactttctct	tggttaggcc	aactcaggat	acttgatctc	ggccttaatg	aaattgaaca	1380
aaaactcagc	ggccaggaat	ggagaggtct	gagaaatata	tttgagatct	acctatccta	1440
taacaaatac	ctccaactgt	ctaccagttc	ctttgcattg	gtccccagcc	ttcaaagact	1500
gatgctcagg	aggggtggcc	ttaaaaatgt	ggatatctcc	ccttcacctt	tccgccctct	1560
tcgtaacttg	accattctgg	acttaagcaa	caacaacata	gccaacataa	atgaggactt	1620
gctggagggg	cttgagaatc	tagaaatcct	ggattttcag	cacaataact	tagccaggct	1680
ctggaaacgc	gcaaaccctg	gtgggtcccg	taatttcctg	aaggggctgt	ctcacctcca	1740
catcttgaat	ttagagtcca	acggcttaga	tgaaatccca	gtcgggggtt	tcaagaactt	1800
attcgaacta	aagagcatca	atctaggact	gaataactta	aacaaacttg	aaccattcat	1860
ttttgatgac	cagacatctc	taaggtcact	gaacctccag	aagaacctca	taacatctgt	1920
tgagaaggat	gttttcgggc	cgccttttca	aaacctgaac	agtttagata	tgcgcttcaa	1980
tccgttcgac	tgcacgtgtg	aaagtatttc	ctggtttggt	aactggatca	accagaccca	2040
cactaatatc	tttgagctgt	ccactcacta	cctctgtaac	actccacatc	attattatgg	2100
cttccccctg	aagcttttct	atacatcatc	ctgtaaagac	agcgccccct	ttgaactcct	2160
cttcataatc	agcaccagta	tgctcctggg	ttttataact	gtgggtactgc	tcattcacat	2220
cgagggctgg	aggatctctt	tttactggaa	tgtttcagtg	catcggaatt	ttggtttcaa	2280
ggaaatagac	acacaggctg	agcagtttga	atatacagcc	tacataattc	atgcccataa	2340
agacagagac	tgggtctggg	aacatttctc	cccaatggaa	gaacaagacc	aatctctcaa	2400
attttgccta	gaagaaaggg	actttgaagc	aggcgtcctt	ggacttgaag	caattgttaa	2460
tagcatcaaa	agaagccgaa	aaatcatttt	cgttatcaca	caccatttat	taaaagaccc	2520
tctgtgcaga	agattcaagg	tacatcacgc	agttcagcaa	gctattgagc	aaaatctgga	2580
ttcaattata	ctgatttttc	tccagaatat	tccagattat	aaactaaacc	atgcactctg	2640

```

tttgcgaaga ggaatgttta aatctcattg catcttgaac tggccagttc agaaagaacg 2700
gataaatgcc tttcatcata aattgcaagt agcacttgga tctcggaatt cagcacatta 2760
aactcatttg aagatttgga gtcggtaaag ggatagatcc aatttataaa ggtccatcat 2820
gaatctaagt tttacttgaa agttttgtat atttatttat atgtatagat gatgatatta 2880
catcacaatc caatctcagt tttgaaatat ttcggcttat ttcattgaca tctggtttat 2940
tcactccaaa taaacacatg ggcagttaaa aacatcctct attaatagat taccatttaa 3000
ttcttgaggt gtatcacagc tttaaagggt tttaaatttt tttatataaa taagactgag 3060
agttttataa atgtaatttt ttaaaactcg agtcttactg tgtagctcag aaaggcctgg 3120
aaattaatat attagagagt catgtcttga acttatttat ctctgcctcc ctctgtctcc 3180
agagtgttgc ttttaagggc atgtagcacc acaccagct atgtacgtgt gggattttat 3240
aatgctcatt tttgagacgt ttatagaata aaagataatt gcttttatgg tataaggcta 3300
cttgaggtaa 3310

```

<210> 10
 <211> 905
 <212> PRT
 <213> murine

<400> 10

```

Met Lys Gly Cys Ser Ser Tyr Leu Met Tyr Ser Phe Gly Gly Leu Leu
1           5           10           15

Ser Leu Trp Ile Leu Leu Val Ser Ser Thr Asn Gln Cys Thr Val Arg
20           25           30

Tyr Asn Val Ala Asp Cys Ser His Leu Lys Leu Thr His Ile Pro Asp
35           40           45

Asp Leu Pro Ser Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu
50           55           60

Arg Arg Leu Pro Pro Thr Asn Phe Thr Arg Tyr Ser Gln Leu Ala Ile
65           70           75           80

Leu Asp Ala Gly Phe Asn Ser Ile Ser Lys Leu Glu Pro Glu Leu Cys
85           90           95

Gln Ile Leu Pro Leu Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu
100          105          110

Ser Gln Ile Ser Asp'Gln Thr Phe Val Phe Cys Thr Asn Leu Thr Glu
115          120          125

Leu Asp Leu Met Ser Asn Ser Ile His Lys Ile Lys Ser Asn Pro Phe
130          135          140

Lys Asn Gln Lys Asn Leu Ile Lys Leu Asp Leu Ser His Asn Gly Leu
145          150          155          160

```

Ser Ser Thr Lys Leu Gly Thr Gly Val Gln Leu Glu Asn Leu Gln Glu
 165 170 175
 Leu Leu Leu Ala Lys Asn Lys Ile Leu Ala Leu Arg Ser Glu Glu Leu
 180 185 190
 Glu Phe Leu Gly Asn Ser Ser Leu Arg Lys Leu Asp Leu Ser Ser Asn
 195 200 205
 Pro Leu Lys Glu Phe Ser Pro Gly Cys Phe Gln Thr Ile Gly Lys Leu
 210 215 220
 Phe Ala Leu Leu Leu Asn Asn Ala Gln Leu Asn Pro His Leu Thr Glu
 225 230 235 240
 Lys Leu Cys Trp Glu Leu Ser Asn Thr Ser Ile Gln Asn Leu Ser Leu
 245 250 255
 Ala Asn Asn Gln Leu Leu Ala Thr Ser Glu Ser Thr Phe Ser Gly Leu
 260 265 270
 Lys Trp Thr Asn Leu Thr Gln Leu Asp Leu Ser Tyr Asn Asn Leu His
 275 280 285
 Asp Val Gly Asn Gly Ser Phe Ser Tyr Leu Pro Ser Leu Arg Tyr Leu
 290 295 300
 Ser Leu Glu Tyr Asn Asn Ile Gln Arg Leu Ser Pro Arg Ser Phe Tyr
 305 310 315 320
 Gly Leu Ser Asn Leu Arg Tyr Leu Ser Leu Lys Arg Ala Phe Thr Lys
 325 330 335
 Gln Ser Val Ser Leu Ala Ser His Pro Asn Ile Asp Asp Phe Ser Phe
 340 345 350
 Gln Trp Leu Lys Tyr Leu Glu Tyr Leu Asn Met Asp Asp Asn Asn Ile
 355 360 365
 Pro Ser Thr Lys Ser Asn Thr Phe Thr Gly Leu Val Ser Leu Lys Tyr
 370 375 380
 Leu Ser Leu Ser Lys Thr Phe Thr Ser Leu Gln Thr Leu Thr Asn Glu
 385 390 395 400
 Thr Phe Val Ser Leu Ala His Ser Pro Leu Leu Thr Leu Asn Leu Thr
 405 410 415
 Lys Asn His Ile Ser Lys Ile Ala Asn Gly Thr Phe Ser Trp Leu Gly
 420 425 430
 Gln Leu Arg Ile Leu Asp Leu Gly Leu Asn Glu Ile Glu Gln Lys Leu
 435 440 445
 Ser Gly Gln Glu Trp Arg Gly Leu Arg Asn Ile Phe Glu Ile Tyr Leu
 450 455 460
 Ser Tyr Asn Lys Tyr Leu Gln Leu Ser Thr Ser Ser Phe Ala Leu Val
 465 470 475 480
 Pro Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val

485 490 495
 Asp Ile Ser Pro Ser Pro Phe Arg Pro Leu Arg Asn Leu Thr Ile Leu
 500 505 510
 Asp Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Glu Asp Leu Leu Glu
 515 520 525
 Gly Leu Glu Asn Leu Glu Ile Leu Asp Phe Gln His Asn Asn Leu Ala
 530 535 540
 Arg Leu Trp Lys Arg Ala Asn Pro Gly Gly Pro Val Asn Phe Leu Lys
 545 550 555 560
 Gly Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Leu Asp
 565 570 575
 Glu Ile Pro Val Gly Val Phe Lys Asn Leu Phe Glu Leu Lys Ser Ile
 580 585 590
 Asn Leu Gly Leu Asn Asn Leu Asn Lys Leu Glu Pro Phe Ile Phe Asp
 595 600 605
 Asp Gln Thr Ser Leu Arg Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr
 610 615 620
 Ser Val Glu Lys Asp Val Phe Gly Pro Pro Phe Gln Asn Leu Asn Ser
 625 630 635 640
 Leu Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ser
 645 650 655
 Trp Phe Val Asn Trp Ile Asn Gln Thr His Thr Asn Ile Phe Glu Leu
 660 665 670
 Ser Thr His Tyr Leu Cys Asn Thr Pro His His Tyr Tyr Gly Phe Pro
 675 680 685
 Leu Lys Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu
 690 695 700
 Leu Leu Phe Ile Ile Ser Thr Ser Met Leu Leu Val Phe Ile Leu Val
 705 710 715 720
 Val Leu Leu Ile His Ile Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn
 725 730 735
 Val Ser Val His Arg Ile Leu Gly Phe Lys Glu Ile Asp Thr Gln Ala
 740 745 750
 Glu Gln Phe Glu Tyr Thr Ala Tyr Ile Ile His Ala His Lys Asp Arg
 755 760 765
 Asp Trp Val Trp Glu His Phe Ser Pro Met Glu Glu Gln Asp Gln Ser
 770 775 780
 Leu Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Leu Gly
 785 790 795 800
 Leu Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe
 805 810 815
 Val Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Arg Arg Phe Lys

	820		825		830										
Val	His	His	Ala	Val	Gln	Gln	Ala	Ile	Glu	Gln	Asn	Leu	Asp	Ser	Ile
	835						840					845			
Ile	Leu	Ile	Phe	Leu	Gln	Asn	Ile	Pro	Asp	Tyr	Lys	Leu	Asn	His	Ala
	850					855					860				
Leu	Cys	Leu	Arg	Arg	Gly	Met	Phe	Lys	Ser	His	Cys	Ile	Leu	Asn	Trp
	865				870					875					880
Pro	Val	Gln	Lys	Glu	Arg	Ile	Asn	Ala	Phe	His	His	Lys	Leu	Gln	Val
			885						890					895	
Ala	Leu	Gly	Ser	Arg	Asn	Ser	Ala	His							
		900					905								

<210> 11
 <211> 3811
 <212> DNA
 <213> Homo sapiens

<400> 11
 acagggccac tgctgctcac agaagcagtg aggatgatgc caggatgatg tctgcctcgc 60
 gcctggctgg gactctgac ccagccatgg ccttcctctc ctgcgtgaga ccagaaagct 120
 gggagccctg cgtggagact tggccctaaa ccacacagaa gagctggcat gaaaccaga 180
 gctttcagac tccggagcct cagcccttca ccccgattcc attgcttctt gctaaatgct 240
 gccgttttat cacggaggtg gttcctaata ttacttatca atgcatggag ctgaatttct 300
 acaaaatccc cgacaacctc cccttctcaa ccaagaacct ggacctgagc tttaatcccc 360
 tgaggcattt aggcagctat agcttcttca gtttccaga actgcaggtg ctggatttat 420
 ccagggtgtga aatccagaca attgaagatg gggcatatca gagcctaagc cacctctcta 480
 ccttaatatt gacaggaaac cccatccaga gtttagccct gggagccttt tctggactat 540
 caagtttaca gaagctggtg gctgtggaga caaatctagc atctctagag aacttcccc 600
 ttggacatct caaaactttg aaagaactta atgtggctca caatcttatc caatctttca 660
 aattacctga gtatttttct aatctgacca atctagagca cttggacctt tccagcaaca 720
 agattcaaag tattttattgc acagacttgc gggttctaca tcaaagccc ctactcaatc 780
 tctctttaga cctgtccctg aaccctatga actttatcca accaggtgca tttaaagaaa 840
 ttaggcttca taagctgact ttaagaaata attttgatag tttaaatgta atgaaaactt 900
 gtattcaagg tctggctggt ttagaagtcc atcgtttggg tctgggagaa tttagaaatg 960
 aaggaaactt ggaaaagttt gacaaatctg ctctagaggg cctgtgcaat ttgaccattg 1020
 aagaattccg attagcatat ttagactact acctcgatga tattattgac ttatttaatt 1080
 gtttgacaaa tgtttcttca ttttccctgg tgagtgtgac tattgaaagg gtaaaagact 1140
 tttcttataa tttcggatgg caacatttag aattagttaa ctgtaaattt ggacagtttc 1200

ccacattgaa actcaaactct ctcaaaaggc ttactttcac ttccaacaaa ggtgggaatg 1260
ctttttcaga agttgatcta ccaagccttg agtttctaga tctcagtaga aatggcttga 1320
gtttcaaagg ttgctgttct caaagtgatt ttgggacaac cagcctaaag tatttagatc 1380
tgagcttcaa tgggtgttatt accatgagtt caaacttctt gggcttagaa caactagaac 1440
atctggatct ccagcattec aatttgaaac aaatgagtga gttttcagta ttcctatcac 1500
tcagaaacct catttacctt gacatttctc atactcacac cagagttgct ttcaatggca 1560
tcttcaatgg cttgtccagt ctggaagtct tgaaaatggc tggcaattct ttccaggaaa 1620
acttccttcc agatatcttc acagagctga gaaacttgac cttcctggac ctctctcagt 1680
gtcaactgga gcagttgtct ccaacagcat ttaactcact ctccagtctt caggtactaa 1740
atatgagcca caacaacttc ttttcattgg atacgtttcc ttataagtgt ctgaactccc 1800
tccaggttct tgattacagt ctcaatcaca taatgacttc caaaaaacag gaactacagc 1860
atttccaag tagtctagct ttcttaaact ttactcagaa tgactttgct tgtacttggtg 1920
aacaccagag tttcctgcaa tggatcaagg accagaggca gctcttggtg gaagttgaac 1980
gaatggaatg tgcaaacacct tcagataagc agggcatgcc tgtgtgaggt ttgaatatca 2040
cctgtcagat gaataagacc atcattgggtg tgtcggtcct cagtgtgctt gtagtatctg 2100
ttgtagcagt tctggtctat aagttctatt ttcacctgat gcttcttgct ggctgcataa 2160
agtatggtag aggtgaaaac atctatgatg cctttgttat ctactcaagc caggatgagg 2220
actgggtaag gaatgagcta gtaaagaatt tagaagaagg ggtgcctcca tttcagctct 2280
gccttacta cagagacttt attcccgggtg tggccattgc tgccaacatc atccatgaag 2340
gtttccataa aagccgaaaag gtgattgttg tgggtgtcca gcacttcac cagagccgct 2400
gggtgatctt tgaatatgag attgctcaga cctggcagtt tctgagcagt cgtgctggta 2460
tcactttcat tgtcctgcag aaggtggaga agaccctgct caggcagcag gtggagctgt 2520
accgccttct cagcaggaac acttacctgg agtgggagga cagtgtcctg gggcggcaca 2580
tcttctggag acgactcaga aaagccctgc tggatggtaa atcatggaat ccagaaggaa 2640
cagtgggtac aggatgcaat tggcaggaag caacatctat ctgaagagga aaaataaaaa 2700
cctcctgagg catttcttgc ccagctgggt ccaacacttg ttcagttaat aagtattaaa 2760
tgctgccaca tgtcaggcct tatgctaagg gtgagtaatt ccatgggtgca ctagatatgc 2820
agggtgcta atctcaagga gcttccagt cagagggaaat aaatgctaga ctaaaataca 2880
gagtcttcca ggtgggcatt tcaaccaact cagtcaagga acccatgaca aagaaagtca 2940
tttcaactct tacctcatca agttgaataa agacagagaa aacagaaaga gacattgttc 3000
ttttcctgag tcttttgaat ggaaattgta ttatgttata gccatcataa aaccattttg 3060

gtagttttga ctgaactggg tgttcacttt ttcctttttg attgaataca atttaaattc 3120
 tacttgatga ctgcagtcgt caaggggctc ctgatgcaag atgccccttc cattttaagt 3180
 ctgtctcctt acagagggtta aagtctaatt gctaattcct aaggaaacct gattaacaca 3240
 tgctcacaac catcctgggc attctcgaac atgttctatt ttttaactaa tcaccctga 3300
 tatattttta tttttatata tccagttttc atttttttac gtcttgccca taagctaata 3360
 tcataaataa ggttggttta gacgtgcttc aaatatccat attaaccact atttttcaag 3420
 gaagtattga aaagtacact ctgtcacttt gtcactcgat gtcattccaa agttattgcc 3480
 tactaagtaa tgactgtcat gaaagcagca ttgaaataat ttgtttaaag ggggcactct 3540
 tttaaacggg aagaaaattt ccgcttcctg gtcttatcat ggacaatttg ggctataggc 3600
 atgaaggaag tgggattacc tcaggaagtc accttttctt gattccagaa acatatgggc 3660
 tgataaaccg ggggtgacct catgaaatga gttgcagcag atgtttattt ttttcagaac 3720
 aagtgatgtt tgatggacct atgaatctat ttagggagac acagatggct gggatccctc 3780
 ccctgtacct ttctcactga caggagaact a 3811

<210> 12

<211> 2845

<212> DNA

<213> Homo sapiens

<400> 12

cctctcacc ttagccag aactgctttg aatacaccaa ttgtgtggg gcggctcgag 60
 gaagagaaga caccagtgc tcagaaactg ctcggtcaga cggatgtagc gagccacgca 120
 ttcacagggc cactgctgct cacagaagca gtgaggatga tggcaggatg atgtctgcct 180
 cgcgcctggc tgggactctg atcccagcca tggccttctt ctctgctg agaccagaaa 240
 gctgggagcc ctgctgggag gtgtgaaatc cagacaattg aagatggggc atatcagagc 300
 ctaagccacc tctctacctt aatattgaca ggaaaccca tccagagttt agccctggga 360
 gccttttctg gactatcaag tttacagaag ctggtggctg tggagacaaa tctagcatct 420
 ctagagaact tccccattgg acatctcaaa actttgaaag aacttaattg ggctcacaat 480
 cttatccaat ctttcaaatt acctgagtat ttttctaact tgaccaatct agagcacttg 540
 gacctttcca gcaacaagat tcaaagtatt tattgcacag acttgccggg tctacatcaa 600
 atgcccctac tcaatctctc tttagacctg tccctgaacc ctatgaactt tatccaacca 660
 ggtgcattta aagaaattag gcttcataag ctgactttaa gaaataattt tgatagttaa 720
 aatgtaatga aaacttgat tcaaggtctg gctgggttag aagtcctatg tttggttctg 780
 ggagaattta gaaatgaagg aaacttgga aagtttgaca aatctgctct agagggcctg 840

tgcaatttga	ccattgaaga	attccgatta	gcatacttag	actactacct	cgatgatatt	900
attgacttat	ttaattgttt	gacaaatgtt	tcttcatttt	ccctggtgag	tgtgactatt	960
gaaagggtaa	aagacttttc	ttataatttc	ggatggcaac	atttagaatt	agttaactgt	1020
aaatttggac	agtttccac	attgaaactc	aaatctctca	aaaggcttac	tttcacttcc	1080
aacaaagggtg	ggaatgcttt	ttcagaagtt	gatctacca	gccttgagtt	tctagatctc	1140
agtagaaatg	gcttgagttt	caaagggtgc	tgttctcaaa	gtgattttgg	gacaaccagc	1200
ctaaagtatt	tagatctgag	cttcaatggt	gttattacca	tgagttcaaa	cttcttgggc	1260
ttagaacaac	tagaacatct	ggatttccag	cattccaatt	tgaaacaaat	gagtgagttt	1320
tcagtattcc	tatcactcag	aaacctcatt	taccttgaca	tttctcatac	tcacaccaga	1380
gttgctttca	atggcatctt	caatggcttg	tccagtctcg	aagtcttgaa	aatggctggc	1440
aattctttcc	aggaaaactt	ccttcagat	atcttcacag	agctgagaaa	cttgaccttc	1500
ctggacctct	ctcagtgtca	actggagcag	ttgtctccaa	cagcatttaa	ctcactctcc	1560
agtcttcagg	tactaaatat	gagccacaac	aacttctttt	cattggatac	gtttccttat	1620
aagtgtctga	actccctcca	ggttcttgat	tacagtctca	atcacataat	gacttccaaa	1680
aaacaggaac	tacagcattt	tccaagtagt	ctagctttct	taaatcttac	tcagaatgac	1740
tttgcttgta	cttgtgaaca	ccagagtttc	ctgcaatgga	tcaaggacca	gaggcagctc	1800
ttggtggaag	ttgaacgaat	ggaatgtgca	acaccttcag	ataagcaggg	catgcctgtg	1860
ctgagtttga	atatcacctg	tcagatgaat	aagaccatca	ttggtgtgtc	ggtcctcagt	1920
gtgctttag	tatctgttgt	agcagttctg	gtctataagt	tctattttca	cctgatgctt	1980
cttgctggct	gcataaagta	tggtagaggt	gaaaacatct	atgatgcctt	tgttatctac	2040
tcaagccagg	atgaggactg	ggtaaggaat	gagctagtaa	agaatttaga	agaaggggtg	2100
cctccatttc	agctctgcct	tcaactacaga	gactttattc	ccggtgtggc	cattgctgcc	2160
aacatcatcc	atgaaggttt	ccataaaagc	cgaaagggtga	ttgttgtggt	gtcccagcac	2220
ttcatccaga	gccgctgggt	tatctttgaa	tatgagattg	ctcagacctg	gcagtttctg	2280
agcagtcgtg	ctggtatcat	cttcattgtc	ctgcagaagg	tggagaagac	cctgctcagg	2340
cagcaggtgg	agctgtaccg	ccttctcagc	aggaacactt	acctggagtg	ggaggacagt	2400
gtcctggggc	ggcacatctt	ctggagacga	ctcagaaaag	ccctgctgga	tggtaaatca	2460
tggaatccag	aaggaacagt	gggtacagga	tgcaattggc	aggaagcaac	atctatctga	2520
agaggaaaaa	taaaaacctc	ctgaggcatt	tcttgcccag	ctgggtccaa	cacttgttca	2580
gttaataagt	attaaatgct	gccacatgtc	aggccttatg	ctaaggggtga	gtaattccat	2640
ggtgcactag	atatgcaggg	ctgctaactc	caaggagctt	ccagtgcaga	gggaataaat	2700
gctagactaa	aatacagagt	cttccagggtg	ggcatttcaa	ccaactcagt	caaggaaccc	2760

atgacaaaga aagtcatttc aactcttacc tcatcaagtt gaataaagac agagaaaaca 2820
gaaaaaaaaa aaaaaaaaaa aaaaa 2845

<210> 13
<211> 3767
<212> DNA
<213> Homo sapiens

<400> 13
cctctcacc ctttagcccag aactgctttg aatacaccaa ttgctgtggg gcggctcgag 60
gaagagaaga caccagtgcc tcagaaactg ctcggtcaga cggatgatagc gagccacgca 120
ttcacagggc cactgctgct cacagaagca gtgaggatga tgccaggatg atgtctgcct 180
cgcgcctggc tgggactctg atcccagcca tggccttcct ctctgcgtg agaccagaaa 240
gctggggagc ctgctgtggg acttggccct aaaccacaca gaagagctgg catgaaacct 300
agagctttca gactccggag cctcagccct tcaccccgat tccattgctt cttgctaaat 360
gctgccgttt tatcacggag gtgtgaaatc cagacaattg aagatggggc atatcagagc 420
ctaagccacc tctctacctt aatattgaca ggaaacccca tccagagttt agccctggga 480
gcctttttctg gactatcaag ttacagaag ctggtggctg tggagacaaa tctagcatct 540
ctagagaact tccccattgg acatctcaaa actttgaaag aacttaatgt ggctcacaat 600
cttatccaat ctttcaaatt acctgagtat ttttctaatac tgaccaatct agagcacttg 660
gacctttcca gcaacaagat tcaaagtatt tattgcacag acttgccggg tctacatcaa 720
atgcccctac tcaatctctc tttagacctg tcctgaacc ctatgaactt tatccaacca 780
ggtgcattta aagaaattag gcttcataag ctgactttaa gaaataattt tgatagttta 840
aatgtaatga aaacttgtat tcaaggctctg gctgggttag aagtccatcg tttgggtctg 900
ggagaattta gaaatgaagg aaacttgga aagtttgaca aatctgctct agagggcctg 960
tgcaatttga ccattgaaga attccgatta gcatacttag actactacct cgatgatatt 1020
attgacttat ttaattgttt gacaaatgtt tcttcatttt ccctggtgag tgtgactatt 1080
gaaagggtta aagacttttc ttataatttc ggatggcaac atttagaatt agttaactgt 1140
aaatttggac agtttccac attgaaactc aaatctctca aaaggcttac tttcacttcc 1200
aacaagggtg ggaatgcttt ttcagaagtt gatctaccaa gccttgagtt tctagatctc 1260
agtagaaatg gcttgagttt caaagggtgc tgttctcaaa gtgatttttg gacaaccagc 1320
ctaaagtatt tagatctgag cttcaatggt gttattacca tgagttcaaa cttcttgggc 1380
ttagaacaac tagaacatct ggatttccag cattccaatt tgaacaaaat gagtgagttt 1440
tcagtattcc tatcactcag aaacctcatt taccttgaca tttctcatc tcacaccaga 1500

gttgctttca atggcatctt caatggcttg tccagtctcg aagtcttgaa aatggctggc	1560
aattctttcc agggaaaactt ccttccagat atcttcacag agctgagaaa cttgaccttc	1620
ctggacctct ctcaagtgtca actggagcag ttgtctccaa cagcatttaa ctcaactctcc	1680
agtcttcagg tactaaatat gagccacaac aacttctttt cattggatac gtttccttat	1740
aagtgtctga actccctcca gggtcttgat tacagtctca atcacataat gacttccaaa	1800
aaacaggaac tacagcattt tccaagtagt ctagctttct taaatcttac tcagaatgac	1860
tttgcttgta cttgtgaaca ccagagtttc ctgcaatgga tcaaggacca gaggcagctc	1920
ttggtggaag ttgaacgaat ggaatgtgca acaccttcag ataagcaggg catgcctgtg	1980
ctgagtttga atatcacctg tcagatgaat aagaccatca ttggtgtgtc ggtcctcagt	2040
gtgctttag tagtctgtgt agcagttctg gtctataagt tctattttca cctgatgctt	2100
cttgctggct gcataaagta tggtagaggt gaaaacatct atgatgcctt tgttatctac	2160
tcaagccagg atgaggactg ggtaaggaat gagctagtaa agaatttaga agaaggggtg	2220
cctccatttc agctctgcct tcaactacaga gactttatcc ccggtgtggc cattgctgcc	2280
aacatcatcc atgaaggttt ccataaaagc cgaaagggtga ttgttgtggt gtcccagcac	2340
ttcatccaga gccgctgggt tatctttgaa tatgagattg ctgagacctg gcagtttctg	2400
agcagtcgtg ctggtatcat cttcattgtc ctgcagaagg tggagaagac cctgctcagg	2460
cagcaggtgg agctgtaccg ccttctcagc aggaacactt acctggagtg ggaggacagt	2520
gtcctggggc ggcacatctt ctggagacga ctgagaaaag ccctgctgga tggtaaataca	2580
tggaaatccag aaggaacagt gggtagagga tgcaattggc aggaagcaac atctatctga	2640
agaggaaaaa taaaacctc ctgaggcatt tcttgcccag ctgggtccaa cacttgttca	2700
gttaataagt attaaatgct gccacatgtc aggccttatg ctaagggtga gtaattccat	2760
gggtgcactag atatgcaggg ctgctaactc caaggagctt ccagtgcaga ggaataaat	2820
gctagactaa aatacagagt cttccaggtg ggcatttcaa ccaactcagt caaggaaccc	2880
atgacaaaaga aagtcatttc aactcttacc tcatcaagtt gaataaagac agagaaaaca	2940
gaaagagaca ttgttctttt cctgagtctt ttgaatggaa attgtattat gttatagcca	3000
tcataaaacc attttggttag ttttgactga actgggtggt cactttttcc tttttgattg	3060
aatacaattt aaattctact tgatgactgc agtcgtcaag gggctcctga tgcaagatgc	3120
cccttccatt ttaagtctgt ctccctacag aggttaaagt ctagtggcta attcctaagg	3180
aaacctgatt aacacatgct cacaaccatc ctggtcattc tcgagcatgt tctatttttt	3240
aactaatcac ccctgatata tttttatttt tatatatcca gttttcattt ttttacgtct	3300
tgccataaag ctaatatcat aaataagggt gtttaagacg tgcttcaaat atccatatta	3360
accactattt ttcaaggaag tatggaaaag tacactctgt cactttgtca ctcgatgtca	3420

ttccaaagtt attgcctact aagtaatgac tgtcatgaaa gcagcattga aataatttgt 3480
ttaaaggggg cactctttta aacgggaaga aaatttccgc ttcttggctt tatcatggac 3540
aatttgggct agaggcagga aggaagtggg atgacctcag gaggtcacct tttcttgatt 3600
ccagaaacat atgggctgat aaaccggggg tgacctcatg aaatgagttg cagcagaagt 3660
ttattttttt cagaacaagt gatgtttgat ggacctctga atctcttttag ggagacacag 3720
atggctggga tccctcccct gtacccttct cactgccagg agaacta 3767

<210> 14

<211> 3814

<212> DNA

<213> Homo sapiens

<400> 14

cctctcacc tttagcccag aactgctttg aatacaccaa ttgctgtggg gcggtctgag 60
gaagagaaga caccagtgcc tcagaaactg ctcggtcaga cggatgtagc gagccacgca 120
ttcacagggc cactgctgct cacagaagca gtgaggatga tgccaggatg atgtctgcct 180
cgcgctggc tgggactctg atcccagcca tggccttcct ctctgcgtg agaccagaaa 240
gctgggagcc ctgctgtggg gtggttccta atattactta tcaatgcatg gagctgaatt 300
tctacaaaat ccccgacaac ctcccccttct caaccaagaa cctggacctg agctttaatc 360
ccctgaggca tttaggcagc tatagcttct tcagtttccc agaactgcag gtgctggatt 420
tatccagggtg tgaaatccag acaattgaag atggggcata tcagagccta agccacctct 480
ctaccttaat attgacagga aaccccatcc agagttagc cctgggagcc ttttctggac 540
tatcaagttt acagaagctg gtggctgtgg agacaaatct agcatctcta gagaacttcc 600
ccattggaca tctcaaaact ttgaaagaac ttaatgtggc tcacaatctt atccaatctt 660
tcaaattacc tgagtatttt tctaattctga ccaatctaga gcacttgagc ctttccagca 720
acaagattca aagtatttat tgcacagact tgcgggttct acatcaaatg cccctactca 780
atctctcttt agacctgtcc ctgaacccta tgaactttat ccaaccaggc gcatttaaag 840
aaattaggct tcataagctg actttaagaa ataattttga tagtttaaag gtaatgaaaa 900
cttgatttca aggtctggct ggtttagaag tccatcggtt ggttctggga gaatttagaa 960
atgaaggaaa cttggaaaag tttgacaaat ctgctctaga gggcctgtgc aatttgacca 1020
ttgaagaatt ccgattagca tacttagact actacctga tgatattatt gacttattta 1080
attgtttgac aaatgtttct tcattttccc tggtagagtgt gactattgaa agggtaaaag 1140
actttcttta taatttcgga tggcaacatt tagaattagt taactgtaaa tttggacagt 1200
ttccacatt gaaactcaaa tctctcaaaa ggcttacttt cacttccaac aaagggtggga 1260

atgctttttc	agaagttgat	ctaccaagcc	ttgagtttct	agatctcagt	agaaatggct	1320
tgagtttcaa	aggttgctgt	tctcaaagtg	attttgggac	aaccagccta	aagtatttag	1380
atctgagctt	caatgggtgtt	attaccatga	gttcaaactt	cttgggctta	gaacaactag	1440
aacatctgga	tttccagcat	tccaatttga	aacaaatgag	tgagttttca	gtattcctat	1500
cactcagaaa	cctcattttac	cttgacattt	ctcatactca	caccagagtt	gctttcaatg	1560
gcattcttcaa	tggcttgtcc	agtctcgaag	tcttgaaaat	ggctggcaat	tctttccagg	1620
aaaacttcct	tccagatata	ttcacagagc	tgagaaaactt	gaccttcctg	gacctctctc	1680
agtgtcaact	ggagcagttg	tctccaacag	catttaactc	actctccagt	cttcaggtag	1740
taaatatgag	ccacaacaac	ttcttttcat	tggatacggt	tccttataag	tgtctgaact	1800
ccctccaggt	tcttgattac	agtctcaatc	acataatgac	ttccaaaaaa	caggaactac	1860
agcattttcc	aagtagtcta	gctttcttaa	atcttactca	gaatgacttt	gcttgtactt	1920
gtgaacacca	gagtttcctg	caatggatca	aggaccagag	gcagctcttg	gtggaagttg	1980
aacgaatgga	atgtgcaaca	ccttcagata	agcagggcat	gcctgtgctg	agtttgaata	2040
tcacctgtca	gatgaataag	accatcattg	gtgtgtcggg	cctcagtggt	cttgtagtat	2100
ctgttgtagc	agttctgggc	tataagttct	attttcacct	gatgcttctt	gctggctgca	2160
taaagtatgg	tagagggtgaa	aacatctatg	atgcctttgt	tatctactca	agccaggatg	2220
aggactgggt	aaggaatgag	ctagtaaaga	atttagaaga	aggggtgcct	ccatttcagc	2280
tctgccttca	ctacagagac	tttattcccc	gtgtggccat	tgctgccaac	atcatccatg	2340
aagggtttcca	taaaagccga	aagggtgattg	ttgtgggtgtc	ccagcacttc	atccagagcc	2400
gctggtgtat	ctttgaatat	gagattgctc	agacctggca	gtttctgagc	agtcgtgctg	2460
gtatcatctt	cattgtcctg	cagaagggtg	agaagaccct	gctcaggcag	cagggtggagc	2520
tgtaccgcct	tctcagcagg	aacacttacc	tggagtggga	ggacagtgtc	ctggggcggc	2580
acatcttctg	gagacgactc	agaaaagccc	tgctggatgg	taaatcatgg	aatccagaag	2640
gaacagtggg	tacaggatgc	aattggcagg	aagcaacatc	tatctgaaga	ggaaaaataa	2700
aaacctcctg	aggcatttct	tgcccagctg	ggtccaacac	ttgttcagtt	aataagtatt	2760
aaatgctgcc	acatgtcagg	ccttatgcta	aggggtgagta	attccatggg	gcactagata	2820
tgcagggctg	ctaattctca	ggagcttcca	gtgcagaggg	aataaatgct	agactaaaaa	2880
acagagtctt	ccagggtggg	atttcaacca	actcagtcaa	ggaacccatg	acaaagaaag	2940
tcatttcaac	tcttacctca	tcaagttgaa	taaagacaga	gaaaacagaa	agagacattg	3000
ttcttttcct	gagtcttttg	aatggaaatt	gtattatggt	atagccatca	taaaaccatt	3060
ttggtagttt	tgactgaact	gggtgttcac	tttttccttt	ttgattgaat	acaattttaa	3120
ttctacttga	tgactgcagt	cgtcaagggg	ctcctgatgc	aagatgcccc	ttccatttta	3180

```

agtctgtctc cttacagagg ttaaagtcta gtggctaatt cctaaggaaa cctgattaac 3240
acatgctcac aaccatcctg gtcattctcg agcatgttct attttttaac taatcacccc 3300
tgatatattt ttatttttat atatccagtt ttcatttttt tacgtcttgc ctataagcta 3360
atatcataaa taaggttggt taagacgtgc ttcaaatac catattaacc actatttttc 3420
aaggaagtat ggaaaagtac actctgtcac tttgtcactc gatgtcattc caaagttatt 3480
gcctactaag taatgactgt catgaaagca gcattgaaat aatttgttta aagggggcac 3540
tcttttaaac gggaagaaaa tttccgcttc ctgggtcttat catggacaat ttgggctaga 3600
ggcaggaagg aagtgggatg acctcaggag gtcacctttt cttgattcca gaaacatatg 3660
ggctgataaa cccggggtga cctcatgaaa tgagttgcag cagaagttaa tttttttcag 3720
aacaagtgat gtttgatgga cctctgaatc tctttaggga gacacagatg gctgggatcc 3780
ctcccctgta cccttctcac tgccaggaga acta 3814

```

```

<210> 15
<211> 3934
<212> DNA
<213> Homo sapiens

```

```

<400> 15
cctctcaccc tttagcccag aactgctttg aatacaccaa ttgctgtggg gcggtcgcag 60
gaagagaaga caccagtgcc tcagaaactg ctcggtcaga cggatgatagc gagccacgca 120
ttcacagggc cactgctgct cacagaagca gtgaggatga tgccaggatg atgtctgcct 180
cgcgcctggc tgggactctg atcccagcca tggccttcct ctctgcgtg agaccagaaa 240
gctgggagcc ctgcgtggag acttggccct aaaccacaca gaagagctgg catgaaaccc 300
agagctttca gactccggag cctcagccct tcacccgat tccattgctt cttgctaaat 360
gctgcggttt tatcacggag gtggttccta atattactta tcaatgcatg gagctgaatt 420
tctacaaaat ccccgacaac ctccccttct caaccaagaa cctggacctg agctttaatc 480
ccctgaggca tttaggcagc tatagcttct tcagtttccc agaactgcag gtgctggatt 540
tatccagggtg tgaaatccag acaattgaag atggggcata tcagagccta agccacctct 600
ctaccttaat attgacagga aacccatcc agagttagc cctgggagcc ttttctggac 660
tatcaagttt acagaagctg gtggctgtgg agacaaatct agcatctcta gagaacttcc 720
ccattggaca tctcaaaact ttgaaagaac ttaatgtggc tcacaatctt atccaatctt 780
tcaaattacc tgagtatttt tctaacttga ccaatctaga gcacttggac ctttccagca 840
acaagattca aagtatttat tgcacagact tgcgggttct acatcaaatg cccctactca 900
atctctcttt agacctgtcc ctgaacccta tgaactttat ccaaccagggt gcatttaaag 960

```

aaattaggct	tcataagctg	actttaagaa	ataatTTTga	tagTTTaaat	gtaatgaaaa	1020
cttgTattca	aggTctggct	ggTTtagaag	tccatcgttt	ggTtctggga	gaatttagaa	1080
atgaaggaaa	cttgGaaaag	tttgacaaat	ctgctctaga	gggcctgtgc	aatttgacca	1140
ttgaagaatt	ccgattagca	tacttagact	actacctga	tgatattatt	gacttattta	1200
attgtttgac	aaatgtttct	tcatTTTccc	tggtgagtgt	gactattgaa	agggtaaaag	1260
actTTTctta	taatttcgga	tgGcaacatt	tagaattagt	taactgtaaa	tttgGacagt	1320
ttcccaCatt	gaaactcaaa	tctctcaaaa	ggcttacttt	cacttccaac	aaaggTggga	1380
atgctTTTTc	agaagtTgat	ctaccaagcc	ttgagTTTct	agatctcagt	agaaatggct	1440
tgagTTTcaa	aggTtgctgt	tctcaaagt	atTTTgggac	aaccagccta	aagtatttag	1500
atctgagctt	caatggTgtt	attaccatga	gttcaaactt	cttgGgctta	gaacaactag	1560
aacatctgga	tttccagcat	tccaatttga	aacaaatgag	tgagTTTtca	gtattcctat	1620
cactcgaaaa	cctcatTTac	cttgacattt	ctcatactca	caccagagtt	gctttcaatg	1680
gcatcttcaa	tgGcttgtcc	agtctcgaag	tcttgaaaa	ggctggcaat	tctttccagg	1740
aaaacttCct	tccagatatc	ttcacagagc	tgagaaactt	gaccttCctg	gacctctctc	1800
agtgtcaact	ggagcagttg	tctccaacag	catttaactc	actctccagt	cttcaggtac	1860
taaatatgag	ccacaacaac	ttctTTTcat	tggtacggtt	tccttataag	tgtctgaact	1920
ccctccaggT	tcttgattac	agtctcaatc	acataatgac	ttccaaaaaa	caggaaactac	1980
agcattTTTcc	aagtagtcta	gctttcttaa	atcttactca	gaatgacttt	gcttgtactt	2040
gtgaacacca	gagTTTcctg	caatggatca	aggaccagag	gcagctcttg	gtggaagttg	2100
aacgaatgga	atgtgcaaca	ccttcagata	agcagggcat	gcctgtgctg	agtttgaata	2160
tcacctgtca	gatgaataag	accatcattg	gtgtgtcggt	cctcagtgtg	cttgtagtat	2220
ctgttgtagc	agttctggtc	tataagttct	atTTTcacct	gatgcttctt	gctggctgca	2280
taaagtatgg	tagaggtgaa	aacatctatg	atgcctTTgt	tatctactca	agccaggatg	2340
aggactgggt	aaggaatgag	ctagtaaaga	atTTtagaaga	aggggtgcct	ccatttcagc	2400
tctgccttca	ctacagagac	tttattcccg	gtgtggccat	tgctgccaac	atcatccatg	2460
aaggTTTcca	taaaagccga	aaggTgattg	ttgtggTgtc	ccagcacttc	atccagagcc	2520
gctggTgtat	ctttgaatat	gagattgctc	agacctggca	gtttctgagc	agtcgtgctg	2580
gtatcatctt	cattgtcctg	cagaaggTgg	agaagaccct	gctcaggcag	caggTggagc	2640
tgtaccgcct	tctcagcagg	aacacttacc	tgagTggga	ggacagtgtc	ctggggcggc	2700
acatcttctg	gagacgactc	agaaaagccc	tgtcggatgg	taaatcatgg	aatccagaag	2760
gaacagtggg	tacaggatgc	aattggcagg	aagcaacatc	tatctgaaga	ggaaaaataa	2820
aaacctcctg	aggcatttct	tgcccagctg	ggtccaacac	ttgttcagtt	aataagtatt	2880

```

aaatgctgcc acatgtcagg ccttatgcta aggggtgagta attccatggt gcactagata 2940
tgcaggggctg ctaatctcaa ggagcttcca gtgcagaggg aataaatgct agactaaaat 3000
acagagtctt ccaggtgggc atttcaacca actcagtcaa ggaacccatg acaaagaaag 3060
tcatttcaac tcttacctca tcaagttgaa taaagacaga gaaaacagaa agagacattg 3120
ttcttttcct gagtcttttg aatggaaatt gtattatggt atagccatca taaaaccatt 3180
ttggtagttt tgactgaact ggggtgtcac ttttccttt ttgattgaat acaatttaaa 3240
ttctacttga tgactgcagt cgtcaagggg ctctgatgc aagatgcccc ttccatttta 3300
agtctgtctc cttacagagg ttaaagtcta gtggctaatt cctaaggaaa cctgattaac 3360
acatgtcac aaccatcctg gtcattctcg agcatgttct attttttaac taatcacccc 3420
tgatatattt ttatttttat atatccagtt ttcatTTTTT tacgtcttgc ctataagcta 3480
atatcataaa taaggttggt taagacgtgc ttcaaatac catattaacc actatTTTTT 3540
aaggaagtat ggaaaagtac actctgtcac tttgtcactc gatgtcattc caaagttatt 3600
gcctactaag taatgactgt catgaaagca gcattgaaat aatttgttta aagggggcac 3660
tcttttaaac gggaagaaaa tttccgcttc ctggtcttat catggacaat ttgggctaga 3720
ggcaggaagg aagtgggatg acctcaggag gtcacctttt cttgattcca gaaacatatg 3780
ggctgataaa cccgggggtga cctcatgaaa tgagttgcag cagaagttta tttttttcag 3840
aacaagtgat gtttgatgga cctctgaatc tctttagggg gacacagatg gctgggatcc 3900
ctccccgtga cccttctcac tgccaggaga acta 3934

```

<210> 16

<211> 839

<212> PRT

<213> Homo sapiens

<400> 16

```

Met Met Ser Ala Ser Arg Leu Ala Gly Thr Leu Ile Pro Ala Met Ala
1           5           10          15

```

```

Phe Leu Ser Cys Val Arg Pro Glu Ser Trp Glu Pro Cys Val Glu Val
          20          25          30

```

```

Val Pro Asn Ile Thr Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile
          35          40          45

```

```

Pro Asp Asn Leu Pro Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn
          50          55          60

```

```

Pro Leu Arg His Leu Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu
          65          70          75          80

```

```

Gln Val Leu Asp Leu Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly
          85          90          95

```


Ala Tyr Gln Ser Leu Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn
 100 105 110
 Pro Ile Gln Ser Leu Ala Leu Gly Ala Phe Ser Gly Leu Ser Ser Leu
 115 120 125
 Gln Lys Leu Val Ala Val Glu Thr Asn Leu Ala Ser Leu Glu Asn Phe
 130 135 140
 Pro Ile Gly His Leu Lys Thr Leu Lys Glu Leu Asn Val Ala His Asn
 145 150 155 160
 Leu Ile Gln Ser Phe Lys Leu Pro Glu Tyr Phe Ser Asn Leu Thr Asn
 165 170 175
 Leu Glu His Leu Asp Leu Ser Ser Asn Lys Ile Gln Ser Ile Tyr Cys
 180 185 190
 Thr Asp Leu Arg Val Leu His Gln Met Pro Leu Leu Asn Leu Ser Leu
 195 200 205
 Asp Leu Ser Leu Asn Pro Met Asn Phe Ile Gln Pro Gly Ala Phe Lys
 210 215 220
 Glu Ile Arg Leu His Lys Leu Thr Leu Arg Asn Asn Phe Asp Ser Leu
 225 230 235 240
 Asn Val Met Lys Thr Cys Ile Gln Gly Leu Ala Gly Leu Glu Val His
 245 250 255
 Arg Leu Val Leu Gly Glu Phe Arg Asn Glu Gly Asn Leu Glu Lys Phe
 260 265 270
 Asp Lys Ser Ala Leu Glu Gly Leu Cys Asn Leu Thr Ile Glu Glu Phe
 275 280 285
 Arg Leu Ala Tyr Leu Asp Tyr Tyr Leu Asp Asp Ile Ile Asp Leu Phe
 290 295 300
 Asn Cys Leu Thr Asn Val Ser Ser Phe Ser Leu Val Ser Val Thr Ile
 305 310 315 320
 Glu Arg Val Lys Asp Phe Ser Tyr Asn Phe Gly Trp Gln His Leu Glu
 325 330 335
 Leu Val Asn Cys Lys Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser
 340 345 350
 Leu Lys Arg Leu Thr Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser
 355 360 365
 Glu Val Asp Leu Pro Ser Leu Glu Phe Leu Asp Leu Ser Arg Asn Gly
 370 375 380
 Leu Ser Phe Lys Gly Cys Cys Ser Gln Ser Asp Phe Gly Thr Thr Ser
 385 390 395 400
 Leu Lys Tyr Leu Asp Leu Ser Phe Asn Gly Val Ile Thr Met Ser Ser
 405 410 415
 Asn Phe Leu Gly Leu Glu Gln Leu Glu His Leu Asp Phe Gln His Ser

				420					425					430		
Asn	Leu	Lys	Gln	Met	Ser	Glu	Phe	Ser	Val	Phe	Leu	Ser	Leu	Arg	Asn	
		435					440					445				
Leu	Ile	Tyr	Leu	Asp	Ile	Ser	His	Thr	His	Thr	Arg	Val	Ala	Phe	Asn	
	450					455					460					
Gly	Ile	Phe	Asn	Gly	Leu	Ser	Ser	Leu	Glu	Val	Leu	Lys	Met	Ala	Gly	
465					470					475					480	
Asn	Ser	Phe	Gln	Glu	Asn	Phe	Leu	Pro	Asp	Ile	Phe	Thr	Glu	Leu	Arg	
			485						490					495		
Asn	Leu	Thr	Phe	Leu	Asp	Leu	Ser	Gln	Cys	Gln	Leu	Glu	Gln	Leu	Ser	
			500					505					510			
Pro	Thr	Ala	Phe	Asn	Ser	Leu	Ser	Ser	Leu	Gln	Val	Leu	Asn	Met	Ser	
	515						520					525				
His	Asn	Asn	Phe	Phe	Ser	Leu	Asp	Thr	Phe	Pro	Tyr	Lys	Cys	Leu	Asn	
	530					535					540					
Ser	Leu	Gln	Val	Leu	Asp	Tyr	Ser	Leu	Asn	His	Ile	Met	Thr	Ser	Lys	
545					550					555					560	
Lys	Gln	Glu	Leu	Gln	His	Phe	Pro	Ser	Ser	Leu	Ala	Phe	Leu	Asn	Leu	
			565						570					575		
Thr	Gln	Asn	Asp	Phe	Ala	Cys	Thr	Cys	Glu	His	Gln	Ser	Phe	Leu	Gln	
			580					585					590			
Trp	Ile	Lys	Asp	Gln	Arg	Gln	Leu	Val	Glu	Val	Glu	Arg	Met	Glu		
	595					600					605					
Cys	Ala	Thr	Pro	Ser	Asp	Lys	Gln	Gly	Met	Pro	Val	Leu	Ser	Leu	Asn	
	610					615					620					
Ile	Thr	Cys	Gln	Met	Asn	Lys	Thr	Ile	Ile	Gly	Val	Ser	Val	Leu	Ser	
625					630					635					640	
Val	Leu	Val	Val	Ser	Val	Val	Ala	Val	Leu	Val	Tyr	Lys	Phe	Tyr	Phe	
			645					650						655		
His	Leu	Met	Leu	Leu	Ala	Gly	Cys	Ile	Lys	Tyr	Gly	Arg	Gly	Glu	Asn	
		660						665					670			
Ile	Tyr	Asp	Ala	Phe	Val	Ile	Tyr	Ser	Ser	Gln	Asp	Glu	Asp	Trp	Val	
	675					680					685					
Arg	Asn	Glu	Leu	Val	Lys	Asn	Leu	Glu	Glu	Gly	Val	Pro	Pro	Phe	Gln	
	690					695					700					
Leu	Cys	Leu	His	Tyr	Arg	Asp	Phe	Ile	Pro	Gly	Val	Ala	Ile	Ala	Ala	
705					710					715					720	
Asn	Ile	Ile	His	Glu	Gly	Phe	His	Lys	Ser	Arg	Lys	Val	Ile	Val	Val	
			725					730						735		
Val	Ser	Gln	His	Phe	Ile	Gln	Ser	Arg	Trp	Cys	Ile	Phe	Glu	Tyr	Glu	
		740						745				750				
Ile	Ala	Gln	Thr	Trp	Gln	Phe	Leu	Ser	Ser	Arg	Ala	Gly	Ile	Ile	Phe	

755 760 765
 Ile Val Leu Gln Lys Val Glu Lys Thr Leu Leu Arg Gln Gln Val Glu
 770 775 780
 Leu Tyr Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Ser
 785 790 795 800
 Val Leu Gly Arg His Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu
 805 810 815
 Asp Gly Lys Ser Trp Asn Pro Glu Gly Thr Val Gly Thr Gly Cys Asn
 820 825 830
 Trp Gln Glu Ala Thr Ser Ile
 835

 <210> 17
 <211> 782
 <212> PRT
 <213> Homo sapiens

 <400> 17
 Met Lys Pro Arg Ala Phe Arg Leu Arg Ser Leu Ser Pro Ser Pro Arg
 1 5 10 15
 Phe His Cys Phe Leu Leu Asn Ala Ala Val Leu Ser Arg Arg Cys Glu
 20 25 30
 Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu Ser
 35 40 45
 Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly Ala
 50 55 60
 Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr Asn
 65 70 75 80
 Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu Lys
 85 90 95
 Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro Glu
 100 105 110
 Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser Asn
 115 120 125
 Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln Met
 130 135 140
 Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn Phe
 145 150 155 160
 Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr Leu
 165 170 175
 Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln Gly
 180 185 190
 Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg Asn
 195 200 205

Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu Cys
 210 215 220
 Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr Leu
 225 230 235 240
 Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser Phe
 245 250 255
 Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr Asn
 260 265 270
 Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln Phe
 275 280 285
 Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser Asn
 290 295 300
 Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu Phe
 305 310 315 320
 Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser Gln
 325 330 335
 Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe Asn
 340 345 350
 Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu Glu
 355 360 365
 His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe Ser
 370 375 380
 Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His Thr
 385 390 395 400
 His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser Leu
 405 410 415
 Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu Pro
 420 425 430
 Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser Gln
 435 440 445
 Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser Ser
 450 455 460
 Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp Thr
 465 470 475 480
 Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser Leu
 485 490 495
 Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro Ser
 500 505 510
 Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr Cys
 515 520 525
 Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu Leu

530 535 540
 Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln Gly
 545 550 555 560
 Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr Ile
 565 570 575
 Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala Val
 580 585 590
 Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys Ile
 595 600 605
 Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr Ser
 610 615 620
 Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu Glu
 625 630 635 640
 Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe Ile
 645 650 655
 Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His Lys
 660 665 670
 Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser Arg
 675 680 685
 Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu Ser
 690 695 700
 Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys Thr
 705 710 715 720
 Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn Thr
 725 730 735
 Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp Arg
 740 745 750
 Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu Gly
 755 760 765
 Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
 770 775 780

<210> 18
 <211> 799
 <212> PRT
 <213> Homo sapiens

<400> 18

Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro Phe Ser Thr
 1 5 10 15
 Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu Gly Ser Tyr
 20 25 30
 Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
 35 40 45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
 50 55 60
 Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
 65 70 75 80
 Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr
 85 90 95
 Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu
 100 105 110
 Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro
 115 120 125
 Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser
 130 135 140
 Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln
 145 150 155 160
 Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
 165 170 175
 Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
 180 185 190
 Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
 195 200 205
 Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
 210 215 220
 Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
 225 230 235 240
 Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
 245 250 255
 Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
 260 265 270
 Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
 275 280 285
 Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
 290 295 300
 Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
 305 310 315 320
 Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
 325 330 335
 Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
 340 345 350
 Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe
 355 360 365
 Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu

```

      370              375              380
Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
385              390              395              400

Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
              405              410              415

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
              420              425              430

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
              435              440              445

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
              450              455              460

Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
465              470              475              480

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
              485              490              495

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
              500              505              510

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
              515              520              525

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
              530              535              540

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
545              550              555              560

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
              565              570              575

Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
              580              585              590

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
              595              600              605

Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
              610              615              620

Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
625              630              635              640

Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
              645              650              655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
              660              665              670

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
              675              680              685

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
              690              695              700

Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu

```

705 710 715 720
 Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
 725 730 735

 Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
 740 745 750

 Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
 755 760 765

 Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
 770 775 780

 Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
 785 790 795

<210> 19
 <211> 639
 <212> PRT
 <213> Homo sapiens

<400> 19

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
 1 5 10 15

 Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
 20 25 30

 Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
 35 40 45

 Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
 50 55 60

 Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
 65 70 75 80

 Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
 85 90 95

 Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
 100 105 110

 Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
 115 120 125

 Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
 130 135 140

 Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
 145 150 155 160

 Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
 165 170 175

 Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
 180 185 190

 Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe
 195 200 205

Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu
 210 215 220
 Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
 225 230 235 240
 Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
 245 250 255
 Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
 260 265 270
 Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
 275 280 285
 Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
 290 295 300
 Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
 305 310 315 320
 Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
 325 330 335
 Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
 340 345 350
 Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
 355 360 365
 Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
 370 375 380
 Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
 385 390 395 400
 Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
 405 410 415
 Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
 420 425 430
 Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
 435 440 445
 Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
 450 455 460
 Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
 465 470 475 480
 Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
 485 490 495
 Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
 500 505 510
 Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
 515 520 525
 Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser

530	535	540
Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu		
545	550	555 560
Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys		
	565	570 575
Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn		
	580	585 590
Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp		
	595	600 605
Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu		
	610	615 620
Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile		
625	630	635

<210> 20
 <211> 3866
 <212> DNA
 <213> murine

<400> 20
 ctggttgacag aaaaatgccag gatgatgcct ccctggctcc tggctaggac tctgatcatg 60
 gcactgttct tctcctgcct gacaccagga agcttgaatc cctgcataga ggtagttcct 120
 aatattacct accaatgcat ggatcagaaa ctcagcaaag tccctgatga cattccttct 180
 tcaaccaaga acatagatct gagcttcaac cccttgaaga tcttaaaaag ctatagcttc 240
 tccaattttt cagaacttca gtggctggat ttatccaggt gtgaaattga aacaattgaa 300
 gacaaggcat ggcattggctt acaccacctc tcaaacttga tactgacagg aaaccctatc 360
 cagagttttt cccaggaag tttctctgga ctaacaagtt tagagaatct ggtggctgtg 420
 gagacaaaat tggcctctct agaaagcttc cctattggac agcttataac cttaaagaaa 480
 ctcaatgtgg ctcaaatctt tatacattcc tgtaagttac ctgcatattt ttccaatctg 540
 acgaacctag tacatgtgga tctttcttat aactatattc aaactattac tgtcaacgac 600
 ttacagtttc tacgtgaaaa tccacaagtc aatctctctt tagacatgtc tttgaacca 660
 attgacttca ttcaagacca agcctttcag ggaattaagc tccatgaact gactctaaga 720
 ggtaatttta atagctcaaa tataatgaaa acttgccttc aaaacctggc tggtttacac 780
 gtccatcggg tgatcttggg agaatttaaa gatgaaagga atctggaaat ttttgaacct 840
 tctatcatgg aaggactatg tgatgtgacc attgatgagt tcagggttaac atatacaaat 900
 gatttttcag atgatattgt taagttccat tgcttggcga atgtttctgc aatgtctctg 960
 gcagggtgat ctataaaata tctagaagat gttcctaaac atttcaaag gcaatcctta 1020
 tcaatcatta gatgtcaact taagcagttt ccaactctgg atctaccctt tcttaaaagt 1080

ttgacttttaa	ctatgaacaa	agggctctatc	agtttttaaaa	aagtggccct	accaagtctc	1140
agctatctag	atcttagtag	aaatgcactg	agcttttagtg	gttgctgttc	ttattctgat	1200
ttgggaacaa	acagcctgag	acacttagac	ctcagcttca	atgggtgccat	cattatgagt	1260
gccaatattca	tgggtctaga	agagctgcag	cacctggatt	ttcagcactc	tacttttaaaa	1320
agggtcacag	aattctcagc	gttcttatcc	cttgaaaagc	tactttacct	tgacatctct	1380
tatactaaca	ccaaaattga	cttcgatggg	atatttcttg	gcttgaccag	tctcaacaca	1440
ttaaaaatgg	ctggcaattc	tttcaaagac	aacacccttt	caaattgtctt	tgcaaacaca	1500
acaaacttga	cattcctgga	tctttctaaa	tgtcaattgg	aacaaatata	ttgggggggta	1560
tttgacaccc	tccatagact	tcaattatta	aatatgagtc	acaacaatct	attgtttttg	1620
gattcatccc	attataacca	gctgtattcc	ctcagcactc	ttgattgcag	tttcaatcgc	1680
atagagacat	ctaaaggaat	actgcaacat	tttccaaaga	gtctagcctt	cttcaatctt	1740
actaacaatt	ctgttgcttg	tatatgtgaa	catcagaaat	tctgcagtg	ggcgaaggaa	1800
cagaagcagt	tcttggtgaa	tggtgaacaa	atgacatgtg	caacacctgt	agagatgaat	1860
acctccttag	tggttgattt	taataattct	acctgttata	tgtacaagac	aatcatcagt	1920
gtgtcagtg	tcagtgtgat	tgtggtatcc	actgtagcat	ttctgatata	ccacttctat	1980
tttcacctga	tacttattgc	tggctgtaaa	aagtacagca	gaggagaaag	catctatgat	2040
gcatttgtga	tctactcgag	tcagaatgag	gactgggtga	gaaatgagct	ggtaaagaat	2100
ttagaagaag	gagtgccccg	ctttcacctc	tgcccttact	acagagactt	tattcctggg	2160
gtagccattg	ctgccaacat	catccaggaa	ggcttccaca	agagccggaa	ggttattgtg	2220
gtagtgtcta	gacactttat	tcagagccgt	tggtgtatct	ttgaatatga	gattgtctaa	2280
acatggcagt	ttctgagcag	ccgctctggc	atcatcttca	ttgtccttga	gaagggttag	2340
aagtccttgc	tgaggcagca	gggtggaattg	tatcgccctc	ttagcagaaa	cacctacctg	2400
gaatgggagg	acaatcctct	ggggaggcac	atcttcttga	gaagacttaa	aaatgcccta	2460
ttggatggaa	aagcctcgaa	tcctgagcaa	acagcagagg	aagaacaaga	aacggcaact	2520
tggacctgag	gagaacaaaa	ctctggggcc	taaaccctagt	ctgtttgcaa	ttaataaatg	2580
ctacagctca	cctggggctc	tgctatggac	cgagagccca	tggaacacat	ggctgctaag	2640
ctatagcatg	gaccttaccg	ggcagaagga	agtagcactg	acaccttctt	ttccaggggt	2700
atgaattacc	taactcggga	aaagaaacat	aatccagaat	ctttaccttt	aatctgaagg	2760
agaagaggct	aaggcctagt	gagaacagaa	aggagaacca	gtcttctactg	ggccttttga	2820
atacaagcca	tgtcatgttc	tgtgtttcag	ttgctttaga	agagtattga	tagtttcaac	2880
tgaactgaac	ggtttcttac	tttccctttt	ttctactgaa	tgcaatatta	aatagctctt	2940
tttgagaggt	cttcattcca	atttcatctt	ccattttatg	tcattttctt	ttcttttttg	3000

tttttatctg attctataag aaatatgatt gatacacgct cacagatagc ctggccaatc	3060
ctaagaatgc tatatattatt aaatacaatt cctagtatac ttttactttt ataaattcag	3120
ttatcgtttt tcatgccttg actataaaact aatatcataa ataagattgt tacaggatatg	3180
ctaagaaggc ccatatttga ctataatttt ttaagaaagt atataaaata tactttgtca	3240
tattgtcact gaatgtcatt cttaagttat tacctaagtt atggatgtca cagagtcagt	3300
gttaaaaata atttggttga tagaaatatt tttaatcagg agggaaaagt ggagaggggt	3360
gcaggaacag aaatcatgat ttcatcattt attcttgatt tttccggaag ttcacatagc	3420
tgaatgacaa gactacatat gctgcaactg atgttccttc tcatcaagga tactctctga	3480
acttgagaac attttgggga ggaagaaagg tctaacatcc ttttccttca tcattctcat	3540
ttctggacat gccttgtgag atggatcaat gttgggagta cacatttctg ctttcacctt	3600
atctcagtca gcatgaacac tgaatatata atgtcatttc acagtgtgtg tgtgttgtgt	3660
atgtacatat atgaacctgt acatgtgttt aagtttaaag agaaaatagt gtacagagca	3720
gggttatatt tgtgataggg ctttaaatag ttgagctaat tcagaaaagt atggagggtt	3780
cttggtaaac caaaccaaaa gtagaatcat tacaagatct aacaataaaa attttgaaaa	3840
aaaaaaaaa aaaaaaaaaa aaaaaa	3866

<210> 21
 <211> 2520
 <212> DNA
 <213> murine

<400> 21	
atgatgcctc cctggctcct ggctaggact ctgatcatgg cactgttctt ctctgcctg	60
acaccaggaa gcttgaatcc ctgcatagag gtagttccta atattaccta ccaatgcatg	120
gatcagaaac tcagcaaagt ccctgatgac attccttctt caaccaagaa catagatctg	180
agcttcaacc ccttgaagat cttaaaaagc tatagcttct ccaatttttc agaacttcag	240
tggctggatt tatccagggtg tgaaattgaa acaattgaag acaaggcatg gcatggctta	300
caccacctct caaacttgat actgacagga aaccctatcc agagtttttc cccaggaagt	360
ttctctggac taacaagttt agagaatctg gtggctgtgg agacaaaatt ggctctcta	420
gaaagcttcc ctattggaca gcttataacc ttaaagaaac tcaatgtggc tcacaatttt	480
atacattcct gtaagttacc tgcatatttt tccaatctga cgaacctagt acatgtggat	540
ctttcttata actatattca aactattact gtcaacgact tacagtttct acgtgaaaat	600
ccacaagtca atctctcttt agacatatct ttgaacccaa ttgacttcat tcaagaccaa	660
gcctttcagg gaattaagct ccatgaactg actctaagag gtaattttta tagctcaa	720

ataatgaaaa	cttgcccttca	aaacctggct	ggtttacaca	tccatcggtt	gatcttggga	780
gaattttaag	atgaaaggaa	tctggaaatt	tttgaaccct	ctatcatgga	aggactatgt	840
gatgtgacca	ttgatgagtt	caggttaaca	tatacaaattg	atttttcaga	tgatattggt	900
aagtccatt	gcttggcgaa	tgtttctgca	atgtctctgg	cagggtgtatc	tataaaatat	960
ctagaagatg	ttcctaaaca	tttcaaattg	caatccttat	caatcattag	atgtcaactt	1020
aagcagtttc	caactctgga	tctacccttt	cttaaaagtt	tgactttaac	tatgaacaaa	1080
gggtctatca	gttttaaaaa	agtggcccta	ccaagtctca	gctatctaga	tcttagtaga	1140
aatgcactga	gcttttagtg	ttgctgttct	tattctgatt	tggaacaaa	cagcctgaga	1200
cacttagacc	tcagcttcaa	tggtgccatc	attatgagtg	ccaatttcat	gggtctagaa	1260
gagctgcagc	acctggattt	tcagcactct	actttaaaaa	gggtcacaga	attctcagcg	1320
ttcttatccc	ttgaaaagct	actttacctt	gacatctctt	atactaacac	caaaattgac	1380
ttcgatggta	tatttcttgg	cttgaccagt	ctcaacacat	taaaaatggc	tggcaattct	1440
ttcaaagaca	acacccttcc	aaatgtcttt	gcaaacacaa	caaacttgac	attcctggat	1500
ctttctaaat	gtcaattgga	acaaatatct	tggggggtat	ttgacaccct	ccatagactt	1560
caattattaa	atatgagtca	caacaatcta	ttgttttttg	attcatccca	ttataaccag	1620
ctgtattccc	tcagcactct	tgattgcagt	ttcaatcgca	tagagacatc	ttaaaggaata	1680
ctgcaacatt	ttcaaagag	tctagccttc	ttcaatctta	ctaacaattc	tgttgcttgt	1740
atatgtgaac	atcagaaatt	cctgcagtgg	gtcaaggacc	agaagcagtt	cttgggtgaat	1800
gttgaaacaa	tgacatgtgc	aacacctgta	gagatgaata	cctccttagt	gttggatttt	1860
aataattcta	cctgttatat	gtacaagaca	atcatcagtg	tgtcagtggg	cagtgtgatt	1920
gtggtatcca	ctgtagcatt	tctgatatac	cacttctatt	ttcacctgat	acttattgct	1980
ggctgtaaaa	agtacagcag	aggagaaagc	atctatgatg	catttgatg	ctactcgagt	2040
cagaatgagg	actgggtgag	aaatgagctg	gtaaagaatt	tagaagaagg	agtgccccgc	2100
tttcacctct	gccttcacta	cagagacttt	attcctgggtg	tagccattgc	tgccaatatc	2160
atccaggaag	gcttccacaa	gagccggaag	gttattgtgg	tagtgtctag	acactttatt	2220
cagagccgtt	ggtgtatctt	tgaatatgag	attgctcaaa	catggcagtt	tctgagcagc	2280
cactctggca	tcattcttcat	tgtccttgag	aagggtgaga	agtccctgct	gaggcagcag	2340
gtggaattgt	atcgcttctt	tagcagaaac	acctacctgg	aatgggagga	caatcctctg	2400
gggaggcaca	tcttctggag	aagacttaaa	aatgccttat	tggatggaaa	agcctcgaat	2460
cctgagcaaa	cagcagagga	agaacaagaa	acggcaactt	ggacctgagg	agaaccgcgg	2520

<210> 22

<211> 3866

<212> DNA
<213> murine

<400> 22

```

ctggttgcag aaaatgccag gatgatgcct ccctggctcc tggctaggac tctgatcatg      60
gcactgttct tctcctgcct gacaccagga agcttgaatc cctgcataga ggtagttcct      120
aatattacct accaatgcat ggatcagaaa ctacagcaaag tccctgatga cattccttct      180
tcaaccaaga acatagatct gagcttcaac cccttgaaga tcttaaaaag ctatagcttc      240
tccaattttt cagaacttca gtggctggat ttatccaggt gtgaaattga aacaattgaa      300
gacaaggcat ggcatggctt acaccacctc tcaaacttga tactgacagg aaaccctatc      360
cagagttttt cccaggaag tttctctgga ctaacaagtt tagagaatct ggtggctgtg      420
gagacaaaat tggcctctct agaaagcttc cctattggac agcttataac cttaaagaaa      480
ctcaatgtgg ctcaaatctt tatacattcc tgtaagttac ctgcatatct ttccaatctg      540
acgaacctag tacatgtgga tctttcttat aactatattc aaactattac tgtcaacgac      600
ttacagtttc tacgtgaaaa tccacaagtc aatctctctt tagacatgtc tttgaacca      660
attgacttca ttcaagacca agcctttcag ggaattaagc tccatgaact gactctaaga      720
ggtaatttta atagctcaaa tataatgaaa acttgccctc aaaacctggc tggtttacac      780
gtccatcggg tgatcttggg agaatttaaa gatgaaagga atctggaaat ttttgaaccc      840
tctatcatgg aaggactatg tgatgtgacc attgatgagt tcagggttaac atatacaaat      900
gatttttcag atgatattgt taagttccat tgcttggcga atgtttctgc aatgtctctg      960
gcagggtgat ctataaaata tctagaagat gttcctaaac atttcaaag gcaatcctta     1020
tcaatcatta gatgtcaact taagcagttt ccaactctgg atctaccctt tcttaaaagt     1080
ttgactttta ctatgaacaa aggtctatc agttttaaaa aagtggccct accaagtctc     1140
agctatctag atcttagtag aaatgcactg agcttttagt gttgctgttc ttattctgat     1200
ttgggaacaa acagcctgag acacttagac ctacagcttca atgggtgccat cattatgagt     1260
gccaatttca tgggtctaga agagctgcag cacctggatt ttcagcactc tactttaaaa     1320
agggtcacag aattctcagc gttcttatcc cttgaaaagc tactttacct tgacatctct     1380
tatactaaca ccaaaattga cttogatggg atatttcttg gcttgaccag tctcaacaca     1440
ttaaaaatgg ctggcaattc tttcaaagac aacacccttt caaatgtctt tgcaaacaca     1500
acaaacttga cattcctgga tctttctaaa tgtcaattgg aacaaatata ttggggggta     1560
tttgacaccc tccatagact tcaattatta aatatgagtc acaacaatct attgtttttg     1620
gattcatccc attataacca gctgtattcc ctacgactc ttgattgcag tttcaatcgc     1680
atagagacat ctaaaggaat actgcaacat tttccaaaga gtctagcctt cttcaatctt     1740

```

actaacaatt ctgttgcttg tatatgtgaa catcagaaat tcctgcagtg ggtcaaggaa	1800
cagaagcagt tcttggtgaa tgttgaacaa atgacatgtg caacacctgt agagatgaat	1860
acctccttag tgttggattt taataattct acctgttata tgtacaagac aatcatcagt	1920
gtgtcagtggt tcagtgatgat tgtggtatcc actgtagcat ttctgatata ccacttctat	1980
tttcacctga tacttattgc tggctgtaaa aagtacagca gaggagaaag catctatgat	2040
gcatttgtga tctactcgag tcagaatgag gactgggtga gaaatgagct ggtaaagaat	2100
ttagaagaag gagtgtcccg ctttcacctc tgcccttact acagagactt tattcctggt	2160
gtagccattg ctgccaaacat catccaggaa ggcttccaca agagccggaa ggttattgtg	2220
gtagtgtcta gacactttat tcagagccgt tgggtgtatct ttgaatatga gattgctcaa	2280
acatggcagt ttctgagcag ccgctctggc atcatcttca ttgtccttga gaaggttgag	2340
aagtccctgc tgaggcagca ggtggaattg tatcgccctc ttagcagaaa cacctacctg	2400
gaatgggagg acaatcctct ggggaggcac atcttctgga gaagacttaa aaatgcccta	2460
ttggatggaa aagcctcgaa tcctgagcaa acagcagagg aagaacaaga aacggcaact	2520
tggacctgag gagaacaaaa ctctggggcc taaaccaggt ctgtttgcaa ttaataaatg	2580
ctacagctca cctggggctc tgctatggac cgagagccca tggaacacat ggctgctaag	2640
ctatagcatg gaccttaccg ggcagaagga agtagcactg acaccttctt ttccaggggt	2700
atgaattacc taactcgga aaagaaacat aatccagaat ctttaccttt aatctgaagg	2760
agaagaggct aaggcctagt gagaacagaa aggagaacca gtcttctactg ggccttttga	2820
atacaagcca tgtcatgttc tgtgtttcag ttgctttaga agagtattga tagtttcaac	2880
tgaactgaac ggtttcttac tttccctttt ttctactgaa tgcaatatta aatagctctt	2940
tttgagaggt cttcattcca atttcatctt ccattttatg tcattttctt ttcttttttg	3000
tttttatcta attctataag aaatatgatt gatacacgct cacagatagc ctggccaatc	3060
ctaagaatgc tatattttatt aaatacaatt cctagtatac ttttactttt ataaattcag	3120
ttatcgtttt tcatgccttg actataaact aatatcataa ataagattgt tacaggatg	3180
ctaagaaggc ccatatttga ctataatttt ttaagaaagt atataaaata tactttgtca	3240
tattgtcact gaatgtcatt cttaagttat tacctaagtt atggatgtca cagagtcagt	3300
gttaaaaata atttggttga tagaaatatt tttaatcagg agggaaaagt ggagaggggt	3360
gcaggaacag aaatcatgat ttcattcattt attcttgatt tttccggaag ttcacatagc	3420
tgaatgacaa gactacatat gctgcaactg atgttccttc tcatcaagga tactctctga	3480
acttgagaac attttgggga ggaagaaagg tctaactcc ttttccttca tcattctcat	3540
ttctggacat gccttggtgag atggatcaat gttgggagta cacatttctg ctttcacctt	3600
atttcagtca gcatgaacac tgaatatata atgtcatttc acagtgtgtg tgtgtgtgtg	3660

atgtacatat atgaacctgt acatgtgttt aagtttaaag agaaaatagt gtacagagca 3720
 ggtgtatatt tgtgataggg ctttaaataag ttgagctaata tcagaaaagt atggagggttt 3780
 cttggtaaac caaaccaaaa gtagaatcat tacaagatct aacaataaaa attttgaaaa 3840
 aaaaaaaaaa aaaaaaaaaa aaaaaa 3866

<210> 23
 <211> 835
 <212> PRT
 <213> murine

<400> 23

Met Met Pro Pro Trp Leu Leu Ala Arg Thr Leu Ile Met Ala Leu Phe
 1 5 10 15
 Phe Ser Cys Leu Thr Pro Gly Ser Leu Asn Pro Cys Ile Glu Val Val
 20 25 30
 Pro Asn Ile Thr Tyr Gln Cys Met Asp Gln Lys Leu Ser Lys Val Pro
 35 40 45
 Asp Asp Ile Pro Ser Ser Thr Lys Asn Ile Asp Leu Ser Phe Asn Pro
 50 55 60
 Leu Lys Ile Leu Lys Ser Tyr Ser Phe Ser Asn Phe Ser Glu Leu Gln
 65 70 75 80
 Trp Leu Asp Leu Ser Arg Cys Glu Ile Glu Thr Ile Glu Asp Lys Ala
 85 90 95
 Trp His Gly Leu His His Leu Ser Asn Leu Ile Leu Thr Gly Asn Pro
 100 105 110
 Ile Gln Ser Phe Ser Pro Gly Ser Phe Ser Gly Leu Thr Ser Leu Glu
 115 120 125
 Asn Leu Val Ala Val Glu Thr Lys Leu Ala Ser Leu Glu Ser Phe Pro
 130 135 140
 Ile Gly Gln Leu Ile Thr Leu Lys Lys Leu Asn Val Ala His Asn Phe
 145 150 155 160
 Ile His Ser Cys Lys Leu Pro Ala Tyr Phe Ser Asn Leu Thr Asn Leu
 165 170 175
 Val His Val Asp Leu Ser Tyr Asn Tyr Ile Gln Thr Ile Thr Val Asn
 180 185 190
 Asp Leu Gln Phe Leu Arg Glu Asn Pro Gln Val Asn Leu Ser Leu Asp
 195 200 205
 Met Ser Leu Asn Pro Ile Asp Phe Ile Gln Asp Gln Ala Phe Gln Gly
 210 215 220
 Ile Lys Leu His Glu Leu Thr Leu Arg Gly Asn Phe Asn Ser Ser Asn
 225 230 235 240

Ile Met Lys Thr Cys Leu Gln Asn Leu Ala Gly Leu His Val His Arg
 245 250 255
 Leu Ile Leu Gly Glu Phe Lys Asp Glu Arg Asn Leu Glu Ile Phe Glu
 260 265 270
 Pro Ser Ile Met Glu Gly Leu Cys Asp Val Thr Ile Asp Glu Phe Arg
 275 280 285
 Leu Thr Tyr Thr Asn Asp Phe Ser Asp Asp Ile Val Lys Phe His Cys
 290 295 300
 Leu Ala Asn Val Ser Ala Met Ser Leu Ala Gly Val Ser Ile Lys Tyr
 305 310 315 320
 Leu Glu Asp Val Pro Lys His Phe Lys Trp Gln Ser Leu Ser Ile Ile
 325 330 335
 Arg Cys Gln Leu Lys Gln Phe Pro Thr Leu Asp Leu Pro Phe Leu Lys
 340 345 350
 Ser Leu Thr Leu Thr Met Asn Lys Gly Ser Ile Ser Phe Lys Lys Val
 355 360 365
 Ala Leu Pro Ser Leu Ser Tyr Leu Asp Leu Ser Arg Asn Ala Leu Ser
 370 375 380
 Phe Ser Gly Cys Cys Ser Tyr Ser Asp Leu Gly Thr Asn Ser Leu Arg
 385 390 395 400
 His Leu Asp Leu Ser Phe Asn Gly Ala Ile Ile Met Ser Ala Asn Phe
 405 410 415
 Met Gly Leu Glu Glu Leu Gln His Leu Asp Phe Gln His Ser Thr Leu
 420 425 430
 Lys Arg Val Thr Glu Phe Ser Ala Phe Leu Ser Leu Glu Lys Leu Leu
 435 440 445
 Tyr Leu Asp Ile Ser Tyr Thr Asn Thr Lys Ile Asp Phe Asp Gly Ile
 450 455 460
 Phe Leu Gly Leu Thr Ser Leu Asn Thr Leu Lys Met Ala Gly Asn Ser
 465 470 475 480
 Phe Lys Asp Asn Thr Leu Ser Asn Val Phe Ala Asn Thr Thr Asn Leu
 485 490 495
 Thr Phe Leu Asp Leu Ser Lys Cys Gln Leu Glu Gln Ile Ser Trp Gly
 500 505 510
 Val Phe Asp Thr Leu His Arg Leu Gln Leu Leu Asn Met Ser His Asn
 515 520 525
 Asn Leu Leu Phe Leu Asp Ser Ser His Tyr Asn Gln Leu Tyr Ser Leu
 530 535 540
 Ser Thr Leu Asp Cys Ser Phe Asn Arg Ile Glu Thr Ser Lys Gly Ile
 545 550 555 560
 Leu Gln His Phe Pro Lys Ser Leu Ala Phe Phe Asn Leu Thr Asn Asn

Ser Val Ala Cys Ile Cys Glu His Gln Lys Phe Leu Gln Trp Val Lys
 565 570 575
 580 585 590
 Glu Gln Lys Gln Phe Leu Val Asn Val Glu Gln Met Thr Cys Ala Thr
 595 600 605
 Pro Val Glu Met Asn Thr Ser Leu Val Leu Asp Phe Asn Asn Ser Thr
 610 615 620
 Cys Tyr Met Tyr Lys Thr Ile Ile Ser Val Ser Val Val Ser Val Ile
 625 630 635 640
 Val Val Ser Thr Val Ala Phe Leu Ile Tyr His Phe Tyr Phe His Leu
 645 650 655
 Ile Leu Ile Ala Gly Cys Lys Lys Tyr Ser Arg Gly Glu Ser Ile Tyr
 660 665 670
 Asp Ala Phe Val Ile Tyr Ser Ser Gln Asn Glu Asp Trp Val Arg Asn
 675 680 685
 Glu Leu Val Lys Asn Leu Glu Glu Gly Val Pro Arg Phe His Leu Cys
 690 695 700
 Leu His Tyr Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala Asn Ile
 705 710 715 720
 Ile Gln Glu Gly Phe His Lys Ser Arg Lys Val Ile Val Val Val Ser
 725 730 735
 Arg His Phe Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala
 740 745 750
 Gln Thr Trp Gln Phe Leu Ser Ser Arg Ser Gly Ile Ile Phe Ile Val
 755 760 765
 Leu Glu Lys Val Glu Lys Ser Leu Leu Arg Gln Gln Val Glu Leu Tyr
 770 775 780
 Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Asn Pro Leu
 785 790 795 800
 Gly Arg His Ile Phe Trp Arg Arg Leu Lys Asn Ala Leu Leu Asp Gly
 805 810 815
 Lys Ala Ser Asn Pro Glu Gln Thr Ala Glu Glu Glu Gln Glu Thr Ala
 820 825 830
 Thr Trp Thr
 835

<210> 24
 <211> 835
 <212> PRT
 <213> murine

<400> 24

Met Met Pro Pro Trp Leu Leu Ala Arg Thr Leu Ile Met Ala Leu Phe
 1 5 10 15

Phe Ser Cys Leu Thr Pro Gly Ser Leu Asn Pro Cys Ile Glu Val Val
 20 25 30
 Pro Asn Ile Thr Tyr Gln Cys Met Asp Gln Lys Leu Ser Lys Val Pro
 35 40 45
 Asp Asp Ile Pro Ser Ser Thr Lys Asn Ile Asp Leu Ser Phe Asn Pro
 50 55 60
 Leu Lys Ile Leu Lys Ser Tyr Ser Phe Ser Asn Phe Ser Glu Leu Gln
 65 70 75 80
 Trp Leu Asp Leu Ser Arg Cys Glu Ile Glu Thr Ile Glu Asp Lys Ala
 85 90 95
 Trp His Gly Leu His His Leu Ser Asn Leu Ile Leu Thr Gly Asn Pro
 100 105 110
 Ile Gln Ser Phe Ser Pro Gly Ser Phe Ser Gly Leu Thr Ser Leu Glu
 115 120 125
 Asn Leu Val Ala Val Glu Thr Lys Leu Ala Ser Leu Glu Ser Phe Pro
 130 135 140
 Ile Gly Gln Leu Ile Thr Leu Lys Lys Leu Asn Val Ala His Asn Phe
 145 150 155 160
 Ile His Ser Cys Lys Leu Pro Ala Tyr Phe Ser Asn Leu Thr Asn Leu
 165 170 175
 Val His Val Asp Leu Ser Tyr Asn Tyr Ile Gln Thr Ile Thr Val Asn
 180 185 190
 Asp Leu Gln Phe Leu Arg Glu Asn Pro Gln Val Asn Leu Ser Leu Asp
 195 200 205
 Ile Ser Leu Asn Pro Ile Asp Phe Ile Gln Asp Gln Ala Phe Gln Gly
 210 215 220
 Ile Lys Leu His Glu Leu Thr Leu Arg Gly Asn Phe Asn Ser Ser Asn
 225 230 235 240
 Ile Met Lys Thr Cys Leu Gln Asn Leu Ala Gly Leu His Ile His Arg
 245 250 255
 Leu Ile Leu Gly Glu Phe Lys Asp Glu Arg Asn Leu Glu Ile Phe Glu
 260 265 270
 Pro Ser Ile Met Glu Gly Leu Cys Asp Val Thr Ile Asp Glu Phe Arg
 275 280 285
 Leu Thr Tyr Thr Asn Asp Phe Ser Asp Asp Ile Val Lys Phe His Cys
 290 295 300
 Leu Ala Asn Val Ser Ala Met Ser Leu Ala Gly Val Ser Ile Lys Tyr
 305 310 315 320
 Leu Glu Asp Val Pro Lys His Phe Lys Trp Gln Ser Leu Ser Ile Ile
 325 330 335
 Arg Cys Gln Leu Lys Gln Phe Pro Thr Leu Asp Leu Pro Phe Leu Lys

			340				345				350				
Ser	Leu	Thr	Leu	Thr	Met	Asn	Lys	Gly	Ser	Ile	Ser	Phe	Lys	Lys	Val
			355					360					365		
Ala	Leu	Pro	Ser	Leu	Ser	Tyr	Leu	Asp	Leu	Ser	Arg	Asn	Ala	Leu	Ser
			370					375					380		
Phe	Ser	Gly	Cys	Cys	Ser	Tyr	Ser	Asp	Leu	Gly	Thr	Asn	Ser	Leu	Arg
385						390					395		400		
His	Leu	Asp	Leu	Ser	Phe	Asn	Gly	Ala	Ile	Ile	Met	Ser	Ala	Asn	Phe
			405					410					415		
Met	Gly	Leu	Glu	Glu	Leu	Gln	His	Leu	Asp	Phe	Gln	His	Ser	Thr	Leu
			420					425					430		
Lys	Arg	Val	Thr	Glu	Phe	Ser	Ala	Phe	Leu	Ser	Leu	Glu	Lys	Leu	Leu
435						440					445				
Tyr	Leu	Asp	Ile	Ser	Tyr	Thr	Asn	Thr	Lys	Ile	Asp	Phe	Asp	Gly	Ile
450						455					460				
Phe	Leu	Gly	Leu	Thr	Ser	Leu	Asn	Thr	Leu	Lys	Met	Ala	Gly	Asn	Ser
465						470					475		480		
Phe	Lys	Asp	Asn	Thr	Leu	Ser	Asn	Val	Phe	Ala	Asn	Thr	Thr	Asn	Leu
			485					490					495		
Thr	Phe	Leu	Asp	Leu	Ser	Lys	Cys	Gln	Leu	Glu	Gln	Ile	Ser	Trp	Gly
			500					505					510		
Val	Phe	Asp	Thr	Leu	His	Arg	Leu	Gln	Leu	Leu	Asn	Met	Ser	His	Asn
515						520					525				
Asn	Leu	Leu	Phe	Leu	Asp	Ser	Ser	His	Tyr	Asn	Gln	Leu	Tyr	Ser	Leu
530						535					540				
Ser	Thr	Leu	Asp	Cys	Ser	Phe	Asn	Arg	Ile	Glu	Thr	Ser	Lys	Gly	Ile
545						550					555		560		
Leu	Gln	His	Phe	Pro	Lys	Ser	Leu	Ala	Phe	Phe	Asn	Leu	Thr	Asn	Asn
			565					570					575		
Ser	Val	Ala	Cys	Ile	Cys	Glu	His	Gln	Lys	Phe	Leu	Gln	Trp	Val	Lys
			580					585					590		
Asp	Gln	Lys	Gln	Phe	Leu	Val	Asn	Val	Glu	Gln	Met	Thr	Cys	Ala	Thr
595						600					605				
Pro	Val	Glu	Met	Asn	Thr	Ser	Leu	Val	Leu	Asp	Phe	Asn	Asn	Ser	Thr
610						615					620				
Cys	Tyr	Met	Tyr	Lys	Thr	Ile	Ile	Ser	Val	Ser	Val	Val	Ser	Val	Ile
625						630					635		640		
Val	Val	Ser	Thr	Val	Ala	Phe	Leu	Ile	Tyr	His	Phe	Tyr	Phe	His	Leu
			645					650					655		
Ile	Leu	Ile	Ala	Gly	Cys	Lys	Lys	Tyr	Ser	Arg	Gly	Glu	Ser	Ile	Tyr
			660					665					670		
Asp	Ala	Phe	Val	Ile	Tyr	Ser	Ser	Gln	Asn	Glu	Asp	Trp	Val	Arg	Asn

675 680 685
 Glu Leu Val Lys Asn Leu Glu Glu Gly Val Pro Arg Phe His Leu Cys
 690 695 700
 Leu His Tyr Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala Asn Ile
 705 710 715 720
 Ile Gln Glu Gly Phe His Lys Ser Arg Lys Val Ile Val Val Val Ser
 725 730 735
 Arg His Phe Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala
 740 745 750
 Gln Thr Trp Gln Phe Leu Ser Ser His Ser Gly Ile Ile Phe Ile Val
 755 760 765
 Leu Glu Lys Val Glu Lys Ser Leu Leu Arg Gln Gln Val Glu Leu Tyr
 770 775 780
 Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Asn Pro Leu
 785 790 795 800
 Gly Arg His Ile Phe Trp Arg Arg Leu Lys Asn Ala Leu Leu Asp Gly
 805 810 815
 Lys Ala Ser Asn Pro Glu Gln Thr Ala Glu Glu Glu Gln Glu Thr Ala
 820 825 830
 Thr Trp Thr
 835

<210> 25

<211> 3431

<212> DNA

<213> Homo sapiens

<400> 25

ggcttatagg gctcgagcgg ccgcccgggc aggtatagaa ttcagcggcc gctgaattct 60
 aggggttttca ggagcccagag cgagggcgcc gcttttgcgt ccgggaggag ccaaccgtgg 120
 cgcaggcggc gcggggaggc gtcccagagt ctactctgc cggccaggct ggactgcagt 180
 gacacaatct cggctgactg caaccactgc ctccagggtt caagcgattc tcttgctca 240
 gcctcccaag tagctgggat tacagattga tgttcatgtt cctggcacta ctacaagatt 300
 catactcctg atgtactga caacgtggct tctccacagt caccaaacca gggatgctat 360
 actggacttc cctactctca tctgctccag cccctgacc ttatagttgc ccagctttcc 420
 tggcaattga ctttgcccat caatacacag gatttagcat ccagggaaga tgtcggagcc 480
 tcagatgtta attttctaatt tgagaatgtt ggcgctgtcc gaacctggag acagaaaaac 540
 aaaaagtcct ttctcctgat tcacaaaaaa ataaaatact gactaccatc actgtgatga 600
 gattcctata gtctcaggaa ctgaagtctt taaacaacca gggaccctct gccctagaa 660
 taagaacata ctagaagtcc cttctgctag gacaacgagg atcatgggag accacctgga 720

ccttctccta ggagtgggtgc tcatggcggg tctgtgtttt ggaattcctt cctgtctcctt	780
tgatggccga atagcctttt atcgtttctg caacctcacc caggtcccc aggtcctcaa	840
caccactgag aggtcctgc tgagcttcaa ctatatcagg acagtcaactg cttcatcctt	900
cccctttctg gaacagctgc agctgctgga gctcgggagc cagtataccc ccttgactat	960
tgacaaggag gccttcagaa acctgcccaa ccttagaatc ttggacctgg gaagtagtaa	1020
gataacttc ttgcatccag atgcttttca gggactgttc catctgtttg aacttagact	1080
gtatttctgt ggtctctctg atgctgtatt gaaagatggg tatttcagaa atttaaaggc	1140
tttaactcgc ttggatctat ccaaaaatca gattcgtagc ctttaccttc atccttcatt	1200
tggaagtgg aattccttaa agtccataga ttttctctcc aaccaaatat tccttgatatg	1260
tgaacatgag ctcgagcccc tacaaggga aacgtctctc ttttttagcc tcgcagctaa	1320
tagcttgat agcagagtct cagtggactg gggaaaatgt atgaacccat tcagaaacat	1380
ggtgctggag atactagatg tttctggaaa tggttgaca gtggacatca caggaaactt	1440
tagcaatgcc atcagcaaaa gccaggcctt ctctttgatt cttgccacc acatcatggg	1500
tgccgggttt ggcttcata acatcaaaga tcctgaccag aacacatttg ctggcctggc	1560
cagaagttca gtgagacacc tggatctttc acatgggttt gtcttctccc tgaactcacg	1620
agtctttgag aactcaagg atttgaagg tctgaacctt gcctacaaca agataaataa	1680
gattgcagat gaagcatttt acggacttga caacctcaa gttctcaatt tgtcatataa	1740
ccttctgggg gaactttaca gtctgaattt ctatggacta cctaaggtag cctacattga	1800
tttgcaaaag aatcacattg caataattca agaccaaaca ttcaaattcc tggaaaaatt	1860
acagaccttg gatctccgag acaatgctct tacaaccatt catctttattc caagcatacc	1920
cgatatcttc ttgagtggca ataaactagt gactttgcc aagatcaacc ttacagcgaa	1980
cctcatccac ttatcagaaa acaggctaga aaatctagat attctctact ttcttctacg	2040
ggtacctcat ctccagattc tcattttaaa tcaaaatcgc ttctcctcct gtagtggaga	2100
tcaaaccctc tcagagaatc ccagcttaga acagcttttc cttggagaaa atatgttgca	2160
acttgctgg gaaactgagc tctgttggga tgtttttgag ggactttctc atcttcaagt	2220
tctgtatttg aatcataact atcttaattc ccttccacca ggagtattta gccatctgac	2280
tgcattaagg ggactaagcc tcaactccaa caggctgaca gttctttctc acaatgattt	2340
acctgcta attagagatcc tggacatatc caggaaccag ctcttagctc ctaatcctga	2400
tgtatttgta tcaacttagt tcttgatat aactcataac aagttcattt gtgaatgtga	2460
acttagcact tttatcaatt ggcttaatca caccaatgtc actatagctg ggcctcctgc	2520
agacatatat tgtgtgtacc ctgactcgtt ctctggggtt tccctcttct ctctttccac	2580
ggaagggtgt gatgaagagg aagtcttaaa gtccctaaag ttctcccttt tcattgtatg	2640

```

cactgtcact ctgactctgt tcctcatgac catcctcaca gtcacaaagt tccggggctt 2700
ctgtttttatc tggtataaga cagcccagag actggtgttc aaggaccatc cccagggcac 2760
agaacctgat atgtacaaat atgatgccta tttgtgcttc agcagcaaag acttcacatg 2820
gggtgcagaat gctttgctca aacacctgga cactcaatac agtgaccaa acagattcaa 2880
cctgtgcttt gaagaaagag actttgtccc aggagaaaac cgcattgcca atatccagga 2940
tgccatctgg aacagtagaa agatcgtttg tcttgtgagc agacacttcc ttagagatgg 3000
ctgggtgcctt gaagccttca gttatgccc gggcaggtgc ttatctgacc ttaacagtgc 3060
tctcatcatg gtgggtggtt ggctccttgc ccagtaccag ttgatgaaac atcaatccat 3120
cagaggcttt gtacagaaac agcagtattt gaggtggcct gaggatctcc aggatgttgg 3180
ctgggtttctt cataaactct ctcaacagat actaaagaaa gaaaaagaaa agaagaaaga 3240
caataacatt ccgttgcaaa ctgtagcaac catctcctaa tcaaaggagc aatttccaac 3300
ttatctcaag ccacaaataa ctcttcactt tgtatttgca ccaagttatc attttggggt 3360
cctctctgga ggtttttttt ttctttttgc tactatgaaa acaacataaa tctctcaatt 3420
ttcgatatcaa a 3431

```

<210> 26

<211> 858

<212> PRT

<213> Homo sapiens

<400> 26

```

Met Gly Asp His Leu Asp Leu Leu Leu Gly Val Val Leu Met Ala Gly
1           5           10          15
Pro Val Phe Gly Ile Pro Ser Cys Ser Phe Asp Gly Arg Ile Ala Phe
20          25          30
Tyr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr
35          40          45
Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
50          55          60
Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
65          70          75          80
Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
85          90          95
Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro
100         105         110
Asp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe
115         120         125
Cys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu

```

	130					135					140				
Lys 145	Ala	Leu	Thr	Arg	Leu 150	Asp	Leu	Ser	Lys	Asn 155	Gln	Ile	Arg	Ser	Leu 160
Tyr	Leu	His	Pro	Ser 165	Phe	Gly	Lys	Leu	Asn 170	Ser	Leu	Lys	Ser	Ile	Asp
Phe	Ser	Ser	Asn 180	Gln	Ile	Phe	Leu	Val 185	Cys	Glu	His	Glu	Leu 190	Glu	Pro
Leu	Gln	Gly 195	Lys	Thr	Leu	Ser	Phe 200	Phe	Ser	Leu	Ala	Ala 205	Asn	Ser	Leu
Tyr	Ser	Arg	Val	Ser	Val	Asp 215	Trp	Gly	Lys	Cys	Met 220	Asn	Pro	Phe	Arg
Asn 225	Met	Val	Leu	Glu	Ile 230	Leu	Asp	Val	Ser	Gly 235	Asn	Gly	Trp	Thr	Val 240
Asp	Ile	Thr	Gly	Asn 245	Phe	Ser	Asn	Ala	Ile 250	Ser	Lys	Ser	Gln	Ala 255	Phe
Ser	Leu	Ile	Leu 260	Ala	His	His	Ile	Met 265	Gly	Ala	Gly	Phe	Gly 270	Phe	His
Asn	Ile	Lys 275	Asp	Pro	Asp	Gln	Asn 280	Thr	Phe	Ala	Gly	Leu 285	Ala	Arg	Ser
Ser	Val	Arg	His	Leu	Asp	Leu 295	Ser	His	Gly	Phe	Val 300	Phe	Ser	Leu	Asn
Ser 305	Arg	Val	Phe	Glu	Thr 310	Leu	Lys	Asp	Leu	Lys 315	Val	Leu	Asn	Leu	Ala 320
Tyr	Asn	Lys	Ile	Asn 325	Lys	Ile	Ala	Asp	Glu 330	Ala	Phe	Tyr	Gly	Leu 335	Asp
Asn	Leu	Gln	Val 340	Leu	Asn	Leu	Ser	Tyr 345	Asn	Leu	Leu	Gly	Glu 350	Leu	Tyr
Ser	Ser	Asn 355	Phe	Tyr	Gly	Leu	Pro 360	Lys	Val	Ala	Tyr	Ile 365	Asp	Leu	Gln
Lys	Asn	His	Ile	Ala	Ile	Ile 375	Gln	Asp	Gln	Thr	Phe 380	Lys	Phe	Leu	Glu
Lys 385	Leu	Gln	Thr	Leu	Asp 390	Leu	Arg	Asp	Asn	Ala 395	Leu	Thr	Thr	Ile	His 400
Phe	Ile	Pro	Ser	Ile 405	Pro	Asp	Ile	Phe	Leu 410	Ser	Gly	Asn	Lys	Leu 415	Val
Thr	Leu	Pro	Lys 420	Ile	Asn	Leu	Thr	Ala 425	Asn	Leu	Ile	His	Leu 430	Ser	Glu
Asn	Arg	Leu 435	Glu	Asn	Leu	Asp	Ile 440	Leu	Tyr	Phe	Leu	Leu 445	Arg	Val	Pro
His	Leu	Gln	Ile	Leu	Ile	Leu 455	Asn	Gln	Asn	Arg	Phe 460	Ser	Ser	Cys	Ser
Gly	Asp	Gln	Thr	Pro	Ser	Glu	Asn	Pro	Ser	Leu	Glu	Gln	Leu	Phe	Leu

465 470 475 480
 Gly Glu Asn Met Leu Gln Leu Ala Trp Glu Thr Glu Leu Cys Trp Asp
 485 490 495

 Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu Asn His Asn
 500 505 510

 Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu Thr Ala Leu
 515 520 525

 Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu Ser His Asn
 530 535 540

 Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg Asn Gln Leu
 545 550 555 560

 Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val Leu Asp Ile
 565 570 575

 Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr Phe Ile Asn
 580 585 590

 Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro Ala Asp Ile
 595 600 605

 Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu Phe Ser Leu
 610 615 620

 Ser Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser Leu Lys Phe
 625 630 635 640

 Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe Leu Met Thr
 645 650 655

 Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile Cys Tyr Lys
 660 665 670

 Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly Thr Glu Pro
 675 680 685

 Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys Asp Phe
 690 695 700

 Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln Tyr Ser
 705 710 715 720

 Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe Val Pro
 725 730 735

 Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn Ser Arg
 740 745 750

 Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly Trp Cys
 755 760 765

 Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp Leu Asn
 770 775 780

 Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr Gln Leu
 785 790 795 800

 Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln Tyr Leu

Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His Lys Leu
 805 810 815
 820 825 830
 Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp Asn Asn
 835 840 845
 Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
 850 855

<210> 27
 <211> 858
 <212> PRT
 <213> Homo sapiens

<400> 27

Met Gly Asp His Leu Asp Leu Leu Leu Gly Val Val Leu Met Ala Gly
 1 5 10 15
 Pro Val Phe Gly Ile Pro Ser Cys Ser Phe Asp Gly Arg Ile Ala Phe
 20 25 30
 Tyr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr
 35 40 45
 Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
 50 55 60
 Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
 65 70 75 80
 Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
 85 90 95
 Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro
 100 105 110
 Asp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe
 115 120 125
 Cys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu
 130 135 140
 Lys Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu
 145 150 155 160
 Tyr Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp
 165 170 175
 Phe Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu Pro
 180 185 190
 Leu Gln Gly Lys Thr Leu Ser Phe Phe Ser Leu Ala Ala Asn Ser Leu
 195 200 205
 Tyr Ser Arg Val Ser Val Asp Trp Gly Lys Cys Met Asn Pro Phe Arg
 210 215 220
 Asn Met Val Leu Glu Ile Val Asp Val Ser Gly Asn Gly Trp Thr Val
 225 230 235 240

Asp Ile Thr Gly Asn Phe Ser Asn Ala Ile Ser Lys Ser Gln Ala Phe
 245 250 255
 Ser Leu Ile Leu Ala His His Ile Met Gly Ala Gly Phe Gly Phe His
 260 265 270
 Asn Ile Lys Asp Pro Asp Gln Asn Thr Phe Ala Gly Leu Ala Arg Ser
 275 280 285
 Ser Val Arg His Leu Asp Leu Ser His Gly Phe Val Phe Ser Leu Asn
 290 295 300
 Ser Arg Val Phe Glu Thr Leu Lys Asp Leu Lys Val Leu Asn Leu Ala
 305 310 315 320
 Tyr Asn Lys Ile Asn Lys Ile Ala Asp Glu Ala Phe Tyr Gly Leu Asp
 325 330 335
 Asn Leu Gln Val Leu Asn Leu Ser Tyr Asn Leu Leu Gly Glu Leu Cys
 340 345 350
 Ser Ser Asn Phe Tyr Gly Leu Pro Lys Val Ala Tyr Ile Asp Leu Gln
 355 360 365
 Lys Asn His Ile Ala Ile Ile Gln Asp Gln Thr Phe Lys Phe Leu Glu
 370 375 380
 Lys Leu Gln Thr Leu Asp Leu Arg Asp Asn Ala Leu Thr Thr Ile His
 385 390 395 400
 Phe Ile Pro Ser Ile Pro Asp Ile Phe Leu Ser Gly Asn Lys Leu Val
 405 410 415
 Thr Leu Pro Lys Ile Asn Leu Thr Ala Asn Leu Ile His Leu Ser Glu
 420 425 430
 Asn Arg Leu Glu Asn Leu Asp Ile Leu Tyr Phe Leu Leu Arg Val Pro
 435 440 445
 His Leu Gln Ile Leu Ile Leu Asn Gln Asn Arg Phe Ser Ser Cys Ser
 450 455 460
 Gly Asp Gln Thr Pro Ser Glu Asn Pro Ser Leu Glu Gln Leu Phe Leu
 465 470 475 480
 Gly Glu Asn Met Leu Gln Leu Ala Trp Glu Thr Glu Leu Cys Trp Asp
 485 490 495
 Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu Asn His Asn
 500 505 510
 Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu Thr Ala Leu
 515 520 525
 Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu Ser His Asn
 530 535 540
 Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg Asn Gln Leu
 545 550 555 560
 Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val Leu Asp Ile

Thr	His	Asn	Lys	565	Phe	Ile	Cys	Glu	Cys	570	Glu	Leu	Ser	Thr	575	Phe	Ile	Asn
			580							585						590		
Trp	Leu	Asn	His	Thr	Asn	Val	Thr	Ile	Ala	Gly	Pro	Pro	Ala	Asp	Ile			
		595						600					605					
Tyr	Cys	Val	Tyr	Pro	Asp	Ser	Phe	Ser	Gly	Val	Ser	Leu	Phe	Ser	Leu			
	610					615					620							
Ser	Thr	Glu	Gly	Cys	Asp	Glu	Glu	Glu	Val	Leu	Lys	Ser	Leu	Lys	Phe			
625					630					635					640			
Ser	Leu	Phe	Ile	Val	Cys	Thr	Val	Thr	Leu	Thr	Leu	Phe	Leu	Met	Thr			
				645					650					655				
Ile	Leu	Thr	Val	Thr	Lys	Phe	Arg	Gly	Phe	Cys	Phe	Ile	Cys	Tyr	Lys			
			660					665					670					
Thr	Ala	Gln	Arg	Leu	Val	Phe	Lys	Asp	His	Pro	Gln	Gly	Thr	Glu	Pro			
		675					680					685						
Asp	Met	Tyr	Lys	Tyr	Asp	Ala	Tyr	Leu	Cys	Phe	Ser	Ser	Lys	Asp	Phe			
	690					695					700							
Thr	Trp	Val	Gln	Asn	Ala	Leu	Leu	Lys	His	Leu	Asp	Thr	Gln	Tyr	Ser			
705					710					715					720			
Asp	Gln	Asn	Arg	Phe	Asn	Leu	Cys	Phe	Glu	Glu	Arg	Asp	Phe	Val	Pro			
				725					730					735				
Gly	Glu	Asn	Arg	Ile	Ala	Asn	Ile	Gln	Asp	Ala	Ile	Trp	Asn	Ser	Arg			
		740						745					750					
Lys	Ile	Val	Cys	Leu	Val	Ser	Arg	His	Phe	Leu	Arg	Asp	Gly	Trp	Cys			
	755						760					765						
Leu	Glu	Ala	Phe	Ser	Tyr	Ala	Gln	Gly	Arg	Cys	Leu	Ser	Asp	Leu	Asn			
	770					775					780							
Ser	Ala	Leu	Ile	Met	Val	Val	Val	Gly	Ser	Leu	Ser	Gln	Tyr	Gln	Leu			
785					790					795					800			
Met	Lys	His	Gln	Ser	Ile	Arg	Gly	Phe	Val	Gln	Lys	Gln	Gln	Tyr	Leu			
			805					810						815				
Arg	Trp	Pro	Glu	Asp	Leu	Gln	Asp	Val	Gly	Trp	Phe	Leu	His	Lys	Leu			
		820						825					830					
Ser	Gln	Gln	Ile	Leu	Lys	Lys	Glu	Lys	Glu	Lys	Lys	Lys	Asp	Asn	Asn			
	835						840					845						
Ile	Pro	Leu	Gln	Thr	Val	Ala	Thr	Ile	Ser									
	850					855												

<210> 28

<211> 365

<212> PRT

<213> Homo sapiens

<400> 28

Cys Trp Asp Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu
 1 5 10 15
 Asn His Asn Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu
 20 25 30
 Thr Ala Leu Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu
 35 40 45
 Ser His Asn Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg
 50 55 60
 Asn Gln Leu Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val
 65 70 75 80
 Leu Asp Ile Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr
 85 90 95
 Phe Ile Asn Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro
 100 105 110
 Ala Asp Ile Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu
 115 120 125
 Phe Ser Leu Ser Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser
 130 135 140
 Leu Lys Phe Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe
 145 150 155 160
 Leu Met Thr Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile
 165 170 175
 Cys Tyr Lys Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly
 180 185 190
 Thr Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser
 195 200 205
 Lys Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr
 210 215 220
 Gln Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp
 225 230 235 240
 Phe Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp
 245 250 255
 Asn Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp
 260 265 270
 Gly Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser
 275 280 285
 Asp Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln
 290 295 300
 Tyr Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln
 305 310 315 320
 Gln Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu

				325						330					335				
His	Lys	Leu	Ser	Gln	Gln	Ile	Leu	Lys	Lys	Glu	Lys	Glu	Lys	Lys	Lys				
			340						345					350					
Asp	Asn	Asn	Ile	Pro	Leu	Gln	Thr	Val	Ala	Thr	Ile	Ser							
		355					360					365							

<210> 29

<211> 4286

<212> DNA

<213> murine

<400> 29

ttgaaatctc	acagcccggt	tggttgcagt	gacccacttc	gttgaacata	ttcttcctaa	60
tcctagtact	ttcaatttgc	tctattccct	ggtgtctatg	cattttaaatac	gactatgggg	120
ccattcttcc	ttgaaccacc	acagaagaca	ttagctctct	gggatccttg	tttaatttttt	180
ctcctcttac	atagcaccta	cgcttggaac	atatgccaga	cacatctgtg	agacaccct	240
tgccgctgca	gctcatggat	ggatgctgag	ttccccacg	caccacactt	cagcaggtgg	300
gtgtatttct	gcttcacatt	atactccac	acggccatgc	atgtcaggca	tggagcaggc	360
tcataacca	cttaattaag	gtgatcatat	cagatccttt	atcaagatgc	atagagtgc	420
cagtgcctgt	actatgatct	cggatctttg	ggagatgggc	tagatagagt	ctgggacaga	480
atacagcaga	gaaaccgata	tgtttattgt	ccgatcatca	gctaagcttc	tgggagctag	540
gaatggggct	ccttggaatga	acagaagtaa	aaatgcctcg	tctttatgac	tttcaacttc	600
cctcagcagg	tctggaatgg	gtgaacaaac	actgcctgcg	tgggtgataa	atagcctctt	660
tttgcctgct	gtttgcctg	tttatgggtc	tgggagggaa	cctagaacct	agcacatgct	720
agacaagtcc	tctagcactg	agctatctcc	ccagcttgga	tgaaatatct	gtaaagtact	780
ggtgcccgctg	tgtaaaatat	gcaccattaa	gtgttcaaga	agaaaagact	gggcatttct	840
gttccacca	gacaagaaga	atctgccagc	agaatgtttg	cgcagtcatt	tgagcaaagg	900
ggtccaaggg	acagtaccct	ccagtgcctg	ggacccatgt	gccgagcctc	aggctgtgat	960
gtggtgttgt	ttttaattct	ctcttttccc	ataggatcat	ggcatgtcaa	cttgacttgc	1020
tcataggtgt	gatcttcatg	gccagccccg	tgttggtaat	atctccctgt	tcttcagacg	1080
gcaggatagc	ctttttccga	ggctgtaacc	tcaccagat	tccttgatc	ctcaatacta	1140
ccactgagag	gctcctgctc	agcttcaact	atatcagtat	ggtggttgcc	acatcatttc	1200
cactcctgga	gcggctccag	ttgctggagc	tggggacca	gtatgctaac	ttgaccattg	1260
gtccaggggc	tttcagaaac	ctgcccacac	ttaggatctt	ggacttgggc	caaagccaga	1320
tcgaagtctt	gaatcgagat	gcctttcaag	gtctgcccc	tctcttgga	cttcggctgt	1380
tttctgtgtg	actctccagt	gctgtgttaa	gtgacgggta	cttcagaaat	ctatattcat	1440

tagctcgctt agacctatct ggcaaccaga ttcacagcct ccgcctccat tcttcattcc	1500
gggaactgaa ttccttaagc gacgtaaatt ttgctttcaa ccaaattatc actatatgtg	1560
aagatgaact cgagcctctg cagggcaaaa cactgtcttt ctttggcctc aaattaacta	1620
agctgttcag cagagtctct gtgggctggg agacatgcag gaaccccttc agaggcgtga	1680
ggctagaaac tctagatctt tctgaaaatg gctggacggt ggacatcaca aggaacttca	1740
gcaacatcat ccaggggaagc cagatttctt ctttgattct taaacaccac atcatgggtc	1800
ctggcttttg cttccagaac atcagagatc ctgaccagag cacatttgcc agcctggcca	1860
gaagtctggg gctgcaactg gacctttcgc acggctttat cttctccttg aatcctcgac	1920
tgtttgggac actgaaggat ttgaagatgc tgaaccttgc cttcaacaag ataaacaaga	1980
ttggagagaa tgccttttat gggcttgaca gcctccaggt tctcaatcta tctataatc	2040
ttttggggga actctataat tccaacttct atgggcttcc tagagtagcc tacgttgacc	2100
ttcaaaggaa ccacattggg atcattcaag accaaacatt cagattatta aaaacgttac	2160
aaaccttaga tctccgtgac aatgctctta aggccattgg ttttattcca agcatacaga	2220
tggtcctcct gggaggcaat aagctgggtc atttgccaca catccacttt actgccaaact	2280
tcctagagtt atctgaaaac aggctagaaa acctgtccga cctctacttc ctctgcgag	2340
ccccccagct ccagtttctc atcttgaatc agaatcgctt ttcgtcatgc aaggcagccc	2400
acactccctc ggagaaccca agcttagaac agcttttctt tacagagaat atgctgcagc	2460
tggcctggga gaccggcctc tggtgggatg tttttcaagg cctttcccg ctcagattc	2520
tttacctgag taataactac cttaatttcc ttccacctgg gatatttaac gacctggttg	2580
cattacggat gcttagtctt agtgctaaca agctgaccgt gctctctccg ggcagtttac	2640
ctgctaattt agagattctc gacatatcta gaaatcagct tttgtgtcct gacctgctt	2700
tgttttcttc gcttcgtgtt ttggacataa ctcataacga gttcgtctgc aactgtgaac	2760
ttagcacttt tatctcctgg ctcaacccaa ccaacgtcac cctgttcggc tctcctgcag	2820
acgtgtattg catgtaccct aactcactgc taggggggtc cctctacaac atatccaccg	2880
aagactgcga tgaagaggaa gccatgcggt ccctaaagt ttcccttttc atcctgtgca	2940
cggtcacttt gactctattc ctcgatca caoctgtagt cataaagttc cggggaatct	3000
gtttcctgtg ctataagacc atccagaagc tgggtgttcaa ggacaaggtc tggagtttg	3060
aacctggtgc atatagatat gatgcctact tctgcttcag cagcaaagac tttgaatggg	3120
cacagaatgc tttgctcaaa cacctggatg ctactacag ttcccgaac aggtcaggc	3180
tatgctttga agaaagagac ttcatccgg gggaaaacca tatctccaac atccaggcgg	3240
ctgtctgggg cagcaggaag acggtgtgtc tagtgagcag acacttcttg aaggatggtt	3300
ggtgccctgga ggccttcagg tatgccaga gccggagtct gtctgacctc aagagcatc	3360

```

tcacgcgtggg ggtgggtggga tcgctgtccc agtatcagct gatgagacat gagaccatca 3420
gaggggtttct gcaaaagcaa cagtacttga ggtggcctga agacctccag gatgttggct 3480
ggttttctcga taaactctcc ggatgcattc taaaggaaga aaaaggaaaag aaaagaagca 3540
gttccatcca gttgcgaacc atagcaacca tttcctagca ggagcgcctc ctagcagaag 3600
tgcaagcatc gtagataact ctccacgctt tatccgcaca gccgctgggg gtccttccct 3660
ggagtcattt ttctgacaat gaaaacaaca ccaatctctt gatttttcat gtcaacaggg 3720
agctttgtct tcactgtttt ccaaattggaa agtaagaggt ccagaaagct gcctctaagg 3780
gctctcacct gccattgatg tcctttcagg cccaatgaca tggtttccct ccatcctatt 3840
gcgtactgtc tgctaccag gtaggcaagag caccttgga gaagttacag gcagcttcat 3900
gctttctgtg ctgttcagtt caaaagcagg tgccttgaga atcctgaatt caagcactct 3960
gtagaacatg gacagacaag atgggtcctt ctctggccat aggcattgagg gccagttgct 4020
gaggactgct ctactacac ctaagtgcac aagtataag aagttggaca gatagacaga 4080
tagcagcagt cccattgctg tagccagaat gcacttattt cctgttctga ccctgcaggc 4140
ccagcttttg gggaccacag ccatgttctg cacgggacct ctcaacctgg cattcatgcc 4200
ctttcacgac ttagcacagg cctgcccttc tttcttcccc acaactatac aagagctgtt 4260
gcaaccactg aaaaaaaaaa aaaaaa 4286

```

<210> 30
 <211> 859
 <212> PRT
 <213> murine

<400> 30

```

Met Ala Cys Gln Leu Asp Leu Leu Ile Gly Val Ile Phe Met Ala Ser
1           5           10           15
Pro Val Leu Val Ile Ser Pro Cys Ser Ser Asp Gly Arg Ile Ala Phe
           20           25           30
Phe Arg Gly Cys Asn Leu Thr Gln Ile Pro Trp Ile Leu Asn Thr Thr
           35           40           45
Thr Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Ser Met Val Val Ala
           50           55           60
Thr Ser Phe Pro Leu Leu Glu Arg Leu Gln Leu Leu Glu Leu Gly Thr
           65           70           75           80
Gln Tyr Ala Asn Leu Thr Ile Gly Pro Gly Ala Phe Arg Asn Leu Pro
           85           90           95
Asn Leu Arg Ile Leu Asp Leu Gly Gln Ser Gln Ile Glu Val Leu Asn
           100          105          110

```


Arg Asp Ala Phe Gln Gly Leu Pro His Leu Leu Glu Leu Arg Leu Phe
 115 120 125
 Ser Cys Gly Leu Ser Ser Ala Val Leu Ser Asp Gly Tyr Phe Arg Asn
 130 135 140
 Leu Tyr Ser Leu Ala Arg Leu Asp Leu Ser Gly Asn Gln Ile His Ser
 145 150 155 160
 Leu Arg Leu His Ser Ser Phe Arg Glu Leu Asn Ser Leu Ser Asp Val
 165 170 175
 Asn Phe Ala Phe Asn Gln Ile Phe Thr Ile Cys Glu Asp Glu Leu Glu
 180 185 190
 Pro Leu Gln Gly Lys Thr Leu Ser Phe Phe Gly Leu Lys Leu Thr Lys
 195 200 205
 Leu Phe Ser Arg Val Ser Val Gly Trp Glu Thr Cys Arg Asn Pro Phe
 210 215 220
 Arg Gly Val Arg Leu Glu Thr Leu Asp Leu Ser Glu Asn Gly Trp Thr
 225 230 235 240
 Val Asp Ile Thr Arg Asn Phe Ser Asn Ile Ile Gln Gly Ser Gln Ile
 245 250 255
 Ser Ser Leu Ile Leu Lys His His Ile Met Gly Pro Gly Phe Gly Phe
 260 265 270
 Gln Asn Ile Arg Asp Pro Asp Gln Ser Thr Phe Ala Ser Leu Ala Arg
 275 280 285
 Ser Ser Val Leu Gln Leu Asp Leu Ser His Gly Phe Ile Phe Ser Leu
 290 295 300
 Asn Pro Arg Leu Phe Gly Thr Leu Lys Asp Leu Lys Met Leu Asn Leu
 305 310 315 320
 Ala Phe Asn Lys Ile Asn Lys Ile Gly Glu Asn Ala Phe Tyr Gly Leu
 325 330 335
 Asp Ser Leu Gln Val Leu Asn Leu Ser Tyr Asn Leu Leu Gly Glu Leu
 340 345 350
 Tyr Asn Ser Asn Phe Tyr Gly Leu Pro Arg Val Ala Tyr Val Asp Leu
 355 360 365
 Gln Arg Asn His Ile Gly Ile Ile Gln Asp Gln Thr Phe Arg Leu Leu
 370 375 380
 Lys Thr Leu Gln Thr Leu Asp Leu Arg Asp Asn Ala Leu Lys Ala Ile
 385 390 395 400
 Gly Phe Ile Pro Ser Ile Gln Met Val Leu Leu Gly Gly Asn Lys Leu
 405 410 415
 Val His Leu Pro His Ile His Phe Thr Ala Asn Phe Leu Glu Leu Ser
 420 425 430
 Glu Asn Arg Leu Glu Asn Leu Ser Asp Leu Tyr Phe Leu Leu Arg Val

435 440 445
 Pro Gln Leu Gln Phe Leu Ile Leu Asn Gln Asn Arg Leu Ser Ser Cys
 450 455 460
 Lys Ala Ala His Thr Pro Ser Glu Asn Pro Ser Leu Glu Gln Leu Phe
 465 470 475 480
 Leu Thr Glu Asn Met Leu Gln Leu Ala Trp Glu Thr Gly Leu Cys Trp
 485 490 495
 Asp Val Phe Gln Gly Leu Ser Arg Leu Gln Ile Leu Tyr Leu Ser Asn
 500 505 510
 Asn Tyr Leu Asn Phe Leu Pro Pro Gly Ile Phe Asn Asp Leu Val Ala
 515 520 525
 Leu Arg Met Leu Ser Leu Ser Ala Asn Lys Leu Thr Val Leu Ser Pro
 530 535 540
 Gly Ser Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg Asn Gln
 545 550 555 560
 Leu Leu Cys Pro Asp Pro Ala Leu Phe Ser Ser Leu Arg Val Leu Asp
 565 570 575
 Ile Thr His Asn Glu Phe Val Cys Asn Cys Glu Leu Ser Thr Phe Ile
 580 585 590
 Ser Trp Leu Asn Gln Thr Asn Val Thr Leu Phe Gly Ser Pro Ala Asp
 595 600 605
 Val Tyr Cys Met Tyr Pro Asn Ser Leu Leu Gly Gly Ser Leu Tyr Asn
 610 615 620
 Ile Ser Thr Glu Asp Cys Asp Glu Glu Glu Ala Met Arg Ser Leu Lys
 625 630 635 640
 Phe Ser Leu Phe Ile Leu Cys Thr Val Thr Leu Thr Leu Phe Leu Val
 645 650 655
 Ile Thr Leu Val Val Ile Lys Phe Arg Gly Ile Cys Phe Leu Cys Tyr
 660 665 670
 Lys Thr Ile Gln Lys Leu Val Phe Lys Asp Lys Val Trp Ser Leu Glu
 675 680 685
 Pro Gly Ala Tyr Arg Tyr Asp Ala Tyr Phe Cys Phe Ser Ser Lys Asp
 690 695 700
 Phe Glu Trp Ala Gln Asn Ala Leu Leu Lys His Leu Asp Ala His Tyr
 705 710 715 720
 Ser Ser Arg Asn Arg Leu Arg Leu Cys Phe Glu Glu Arg Asp Phe Ile
 725 730 735
 Pro Gly Glu Asn His Ile Ser Asn Ile Gln Ala Ala Val Trp Gly Ser
 740 745 750
 Arg Lys Thr Val Cys Leu Val Ser Arg His Phe Leu Lys Asp Gly Trp
 755 760 765
 Cys Leu Glu Ala Phe Arg Tyr Ala Gln Ser Arg Ser Leu Ser Asp Leu

770 775 780
 Lys Ser Ile Leu Ile Val Val Val Val Gly Ser Leu Ser Gln Tyr Gln
 785 790 795 800
 Leu Met Arg His Glu Thr Ile Arg Gly Phe Leu Gln Lys Gln Gln Tyr
 805 810 815
 Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu Asp Lys
 820 825 830
 Leu Ser Gly Cys Ile Leu Lys Glu Glu Lys Gly Lys Lys Arg Ser Ser
 835 840 845
 Ser Ile Gln Leu Arg Thr Ile Ala Thr Ile Ser
 850 855

<210> 31
 <211> 3373
 <212> DNA
 <213> Homo sapiens

<400> 31
 agctggctag cggttaaacg ggccctctag actcgagcgg ccgcaattc actagtgtatt 60
 cacctctcat gctctgctct cttcaaccag acctctacat tccatttttg aagaagacta 120
 aaaatgggtg ttccaatgtg gacactgaag agacaaattc ttatcctttt taacataatc 180
 ctaatttcca aactccttgg ggctagatgg tttcctaaaa ctctgccctg tgatgtcact 240
 ctggatgttc caaagaacca tgtgatcgtg gactgcacag acaagcattt gacagaaatt 300
 cctggaggta ttcccacgaa caccacgaac ctaccctca ccattaacca cataccagac 360
 atctccccag cgctcctttca cagactggac catctggtag agatcgattt cagatgcaac 420
 tgtgtaccta ttccactggg gtcaaaaaac aacatgtgca tcaagaggct gcagattaaa 480
 cccagaagct ttagtggact cacttattta aaatcccttt acctggatgg aaaccagcta 540
 ctagagatac cgcagggcct ccgccttagc ttacagcttc tcagccttga ggccaacaac 600
 atcttttcca tcagaaaaga gaatctaaca gaactggcca acatagaaat actctacctg 660
 ggccaaaact gttattatcg aaatccttgt tatgtttcat attcaataga gaaagatgcc 720
 ttcttaaact tgacaaagtt aaaagtgtc tccctgaaag ataacaatgt cacagccgtc 780
 cctactgttt tgccatctac tttaacagaa ctatatctct acaacaacat gattgcaaaa 840
 atccaagaag atgattttta taacctcaac caattacaaa ttcttgacct aagtggaaat 900
 tgccctcggt gttataatgc cccatttcct tgtgcgccgt gtaaaaataa ttctccccta 960
 cagatccctg taaatgcttt tgatgcgctg ~~ccgcaattc~~ ~~aaatctttacg~~ tctacacagt 1020
 aactctcttc agcatgtgcc cccaagatgg ttaagaaca tcaacaaact ccaggaactg 1080
 gatctgtccc aaaacttctt ggccaaagaa attggggatg ctaaatttct gcattttctc 1140
 cccagcctca tccaattgga tctgtcttct aattttgaac ttcaggtcta tcgtgcatct 1200

atgaatctat cacaagcatt ttcttcactg aaaagcctga aaattctgcg gatcagagga 1260
tatgtcttta aagagttgaa aagctttaac ctctcgccat tacataatct tcaaaatctt 1320
gaagtctctg atcttggcac taactttata aaaattgcta acctcagcat gtttaaacia 1380
tttaaaagac tgaaagtcac agatctttca gtgaataaaa taccaccttc aggagattca 1440
agtgaagttg gcttctgctc aaatgccaga acttctgtag aaagttatga accccagggtc 1500
ctggaacaat tacattatct cagatatgat aagtatgcaa ggagttgcag attcaaaaac 1560
aaagaggctt ctttcatgtc tgttaatgaa agctgctaca agtatgggca gaccttggat 1620
ctaagtaaaa atagtatatt ttttgtcaag tcctctgatt ttcagcatct ttctttcctc 1680
aaatgcctga atctgtcagg aaatctcatt agccaaactc ttaatggcag tgaattccaa 1740
ccttttagcag agctgagata tttggacttc tccaacaacc ggcttgattt actccattca 1800
acagcatttg aagagcttca caaactggaa gttctggata taagcagtaa tagccattat 1860
tttcaatcag aaggaattac tcatatgcta aactttacca agaacctaaa ggcttctgcag 1920
aaactgatga tgaacgacaa tgacatctct tcctccacca gcaggaccat ggagagtgag 1980
tctcttagaa ctctggaatt cagaggaaat cacttagatg ttttatggag agaagggtgat 2040
aacagatact tacaattatt caagaatctg ctaaaattag aggaattaga catctctaaa 2100
aattccctaa gtttcttgcc ttctggagtt tttgatggta tgccctcaaa tctaaagaat 2160
ctctctttgg ccaaaaatgg gctcaaactc ttcagttgga agaaactcca gtgtctaaag 2220
aacctggaaa ctttggacct cagccacaac caactgacca ctgtccctga gagattatcc 2280
aactgttcca gaagcctcaa gaatctgatt ctttaagaata atcaaactcag gagtctgacg 2340
aagtattttc tacaagatgc cttccagttg cgatatctgg atctcagctc aaataaaatc 2400
cagatgatcc aaaagaccag cttccagaa aatgtcctca acaatctgaa gatgttgctt 2460
ttgcatcata atcggtttct gtgcacctgt gatgctgtgt ggtttgtctg gtgggttaac 2520
catacggagg tgactattcc ttacctggcc acagatgtga cttgtgtggg gccaggagca 2580
cacaagggcc aaagtgtgat ctccctggat ctgtacacct gtgagttaga tctgactaac 2640
ctgattctgt tctcactttc catatctgta tctctcttcc tcatgggtgat gatgacagca 2700
agtcacctct atttctggga tgtgtggtat atttaccatt tctgtaaggc caagataaag 2760
gggtatcagc gtctaataatc accagactgt tgctatgatg cttttattgt gtatgacact 2820
aaagaccag ctgtgaccga gtggaatctg gtgagctgg tggccaaact ggaagacca 2880
agagagaaac attttaattt atgtctcgag gaaagggact gggtaccagg gcagccagtt 2940
ctggaaaacc tttccagag catacagctt agcaaaaaga cagtgtttgt gatgacagac 3000
aagtatgcaa agactgaaaa ttttaagata gcattttact tgtcccatca gaggctcatg 3060

gatgaaaaag ttgatgtgat tatcttgata tttcttgaga agccttttca gaagtccaag 3120
 ttctccagc tccggaaaag gctctgtggg agttctgtcc ttgagtggcc acaaaccg 3180
 caagctcacc catacttctg gcagtgtcta aagaacgccc tggccacaga caatcatgtg 3240
 gcctatagtc aggtgttcaa ggaaacggtc tagaatcgaa tccccgcggc cgccactgtg 3300
 ctggatatct gcagaattcc accacactgg actagtggat ccgagctcgg taccaagctt 3360
 aagtttaaac cgc 3373

<210> 32

<211> 3416

<212> DNA

<213> Homo sapiens

<400> 32

tccagatata ggatcactcc atgccatcaa gaaagttgat gctattgggc ccatctcaag 60
 ctgatcttgg cacctctcat gctctgtctt cttcaaccag acctctacat tccattttgg 120
 aagaagacta aaaatggtgt ttccaatgtg gacactgaag agacaaattc ttatcctttt 180
 taacataatc ctaatttcca aactccttgg ggctagatgg tttcctaaaa ctctgccttg 240
 tgatgtcact ctggatgttc caaagaacca tgtgatcgtg gactgcacag acaagcattt 300
 gacagaaatt cctggaggta tccccacgaa caccacgaac ctccacctca ccattaacca 360
 cataccagac atctccccag cgtcctttca cagactggac catctggtag agatcgattt 420
 cagatgcaac tgtgtaccta ttccactggg gtcaaaaaac aacatgtgca tcaagaggct 480
 gcagattaaa cccagaagct ttagtggact cacttattta aaatcccttt acctggatgg 540
 aaaccagcta ctagagatac cgcagggcct cccgcctagc ttacagcttc tcagccttga 600
 ggccaacaac atctttttcca tcagaaaaga gaatctaaca gaactggcca acatagaaat 660
 actctacctg ggccaaaact gttattatcg aaatccttgt tatgtttcat attcaataga 720
 gaaagatgcc ttctaaact tgacaaagtt aaaagtgtc tccctgaaag ataacaatgt 780
 cacagccgtc cctactgttt tgccatctac tttaacagaa ctatatctct acaacaacat 840
 gattgcaaaa atccaagaag atgattttta taacctcaac caattacaaa ttcttgacct 900
 aagtggaaat tgccctcgtt gttataatgc cccatttcct tgtgcgccgt gtaaaaataa 960
 ttctccccta cagatccctg taaatgcttt tgatgcgctg acagaattaa aagttttacg 1020
 tctacacagt aactctcttc agcatgtgcc cccaagatgg tttaagaaca tcaacaaact 1080
 ccaggaactg gatctgtccc aaaacttctt ggccaaagaa attggggatg ctaaatttct 1140
 gcattttctc cccagcctca tccaattgga tctgtctttc aattttgaac ttcaggctca 1200
 tcgtgcatct atgaatctat cacaagcatt ttcttcactg aaaagcctga aaattctgcg 1260

gatcagagga	tatgtcttta	aagagttgaa	aagctttaac	ctctcgccat	tacataatct	1320
tcaaaatctt	gaagttcttg	atcttggcac	taactttata	aaaattgcta	acctcagcat	1380
gtttaaacia	tttaaaagac	tgaaagtcac	agatctttca	gtgaataaaa	tatcaccttc	1440
aggagattca	agtgaagttg	gcttctgctc	aaatgccaga	acttctgtag	aaagttatga	1500
accccaggtc	ctggaacaat	tacattatct	cagatatgat	aagtatgcaa	ggagttgcag	1560
attcaaaaac	aaagaggctt	ctttcatgtc	tgtaaatgaa	agctgctaca	agtatgggca	1620
gaccttggat	ctaagtaaaa	atagtatatt	ttttgtcaag	tcctctgatt	ttcagcatct	1680
ttctttcctc	aaatgcctga	atctgtcagg	aaatctcatt	agccaaactc	ttaatggcag	1740
tgaattccaa	ccttttagcag	agttgagata	tttggaacttc	tccaacaacc	ggcttgattt	1800
actccattca	acagcatttg	aagagcttca	caaactggaa	gttctggata	taagcagtaa	1860
tagccattat	tttcaatcag	aaggaattac	tcatatgcta	aaactttacca	agaacctaaa	1920
ggttctgcag	aaactgatga	tgaacgacaa	tgacatctct	tcctccacca	gcaggaccat	1980
ggagagttag	tctcttagaa	ctctggaatt	cagaggaaat	cacttagatg	ttttatggag	2040
agaaggtagt	aacagatact	tacaattatt	caagaatctg	ctaaaattag	aggaattaga	2100
catctctaaa	aattccctaa	gtttcttgcc	ttctggagtt	tttgatggta	tgctccaaa	2160
tctaaagaat	ctctcttttg	ccaaaaatgg	gctcaaactc	ttcagttgga	agaaactcca	2220
gtgtctaaag	aacctggaaa	ctttggacct	cagccacaac	caactgacca	ctgtccctga	2280
gagattatcc	aactgttcca	gaagccacaa	gaatctgatt	cttaagaata	atcaaatcag	2340
gagtccgacg	aagtattttc	tacaagatgc	cttcagttg	cgatatctgg	atctcagctc	2400
aaataaaatc	cagatgatcc	aaaagaccag	cttcccagaa	aatgtcctca	acaatctgaa	2460
gatgttgctt	ttgcatcata	atcggtttct	gtgcacctgt	gatgctgtgt	ggtttgctg	2520
gtgggttaac	catacgagg	tgactattcc	ttacctggcc	acagatgtga	cttggtggg	2580
gccaggagca	cacaagggcc	aaagtgtgat	ctccctggat	ctgtacacct	gtgagttaga	2640
tctgactaac	ctgattctgt	tctcactttc	catatctgta	tctctctttc	tcatggtgat	2700
gatgacagca	agtcacctct	atctctggga	tgtgtgggat	atctaccatt	tctgtaaggc	2760
caagataaag	gggtatcagc	gtctaataatc	accagactgt	tgctatgatg	cttttattgt	2820
gtatgacact	aaagaccag	ctgtgaccga	gtgggttttg	gctgagctgg	tggccaaact	2880
ggaagacca	agagagaaac	attttaattt	atgtctcgag	gaaagggact	ggttaccagg	2940
gcagccagtt	ctggaaaacc	tttcccagag	catacagctt	agcaaaaaga	cagtgtttgt	3000
gatgacagac	aagtatgcaa	agactgaaaa	ttttaagata	gcattttact	tgtcccatca	3060
gaggctcatg	gatgaaaaag	ttgatgtgat	tatcttgata	tttcttgaga	agccctttca	3120
gaagtccaag	ttcctccagc	tcoggaag	gctctgtggg	agttctgtcc	ttgagtggcc	3180

aacaaacccg caagctcacc catacttctg gcagtgtcta aagaacgccc tggccacaga 3240
caatcatgtg gcctatagtc aggtgttcaa ggaaacggtc tagcccttct ttgcaaaaca 3300
caactgccta gtttaccaag gagaggcctg gctgtttaaa ttgttttcat atatatcaca 3360
ccaaaagcgt gttttgaaat tcttcaagaa atgagattgc ccatatttca ggggag 3416

<210> 33

<211> 3418

<212> DNA

<213> Homo sapiens

<400> 33

actccagata taggatcact ccatgccatc aagaaagttg atgctattgg gcccatctca 60
agctgatctt ggcacctctc atgctctgct ctcttcaacc agacctctac attccatttt 120
ggaagaagac taaaaatggg gtttccaatg tggacactga agagacaaat tcttatcctt 180
tttaacataa tcctaatttc caaactcctt ggggctagat ggtttcctaa aactctgccc 240
tgtgatgtca ctctggatgt tccaaagaac catgtgatcg tggactgcac agacaagcat 300
ttgacagaaa ttctggagg tattcccacg aacaccacga acctcaccct caccattaac 360
cacataccag acatctcccc agcgtccttt cacagactgg accatctggg agagatcgat 420
ttcagatgca actgtgtacc tattccactg gggtcacaaa acaacatgtg catcaagagg 480
ctgcagatta aaccagaag ctttagtgga ctcaattatt taaaatccct ttacctggat 540
ggaaaccagc tactagagat accgcagggc ctccgccta gcttacagct tctcagcctt 600
gaggccaaca acatcttttc catcagaaaa gagaatctaa cagaactggc caacatagaa 660
atactctacc tgggccaaaa ctgttattat cgaaatcctt gttatgtttc atattcaata 720
gagaaagatg ccttcctaaa cttgacaaag ttaaaagtgc tctccctgaa agataacaat 780
gtcacagcgg tcctactgt tttgccatct actttaacag aactatatct ctacaacaac 840
atgattgcaa aaatccaaga agatgatttt aataacctca accaattaca aattcttgac 900
ctaagtggaa attgccctcg ttgttataat gcccatttc cttgtgcgcc gtgtaaaaat 960
aattctcccc tacagatccc tgtaaagtgt tttgatgcgc tgacagaatt aaaagtttta 1020
cgtctacaca gtaactctct tcagcatgtg cccccaagat ggtttaagaa catcaacaaa 1080
ctccaggaac tggatctgtc ccaaaacttc ttggccaaag aaattgggga tgctaaattt 1140
ctgcattttc tccccagcct catccaattg gatctgtctt tcaattttga acttcagggtc 1200
tatcgtgcat ctatgaatct atcacaagca ttttcttcac tgaaaagcct gaaaattctg 1260
cggatcagag gatatgtctt taaagagttg aaaagcttta acctctogcc attacataat 1320
cttcaaaaatc ttgaagttct tgatcttggc actaacttta taaaaattgc taacctcagc 1380

atgttttaaac	aattttaaag	actgaaagtc	atagatcttt	cagtgaataa	aatatcacct	1440
tcaggagatt	caagtgaagt	tggtctctgc	tcaaattgcca	gaacttctgt	agaaagtatt	1500
gaacccagg	tcctggaaca	attacattat	ttcagatatg	ataagtatgc	aaggagttgc	1560
agattcaaaa	acaaagaggc	ttctttcatg	tctgttaatg	aaagctgcta	caagtatggg	1620
cagaccttgg	atctaagtaa	aaatagtata	ttttttgtca	agtcctctga	ttttcagcat	1680
ctttctttcc	tcaaattgct	gaatctgtca	ggaaatctca	ttagccaaac	tcttaatggc	1740
agtgaattcc	aacctttagc	agagctgaga	tatttggact	tctccaacaa	ccggcttgat	1800
ttactccatt	caacagcatt	tgaagagctt	cacaaactgg	aagttctgga	tataagcagt	1860
aatagccatt	atthttcaatc	agaaggaatt	actcatatgc	taaactttac	caagaacctt	1920
aaggttctgc	agaaactgat	gatgaacgac	aatgacatct	cttcctccac	cagcaggacc	1980
atggagagtg	agtctcttag	aactctggaa	ttcagaggaa	atcacttaga	tgthtttatgg	2040
agagaaggtg	ataacagata	cttacaatta	ttcaagaatc	tgctaaaatt	agaggaatta	2100
gacatctcta	aaaattccct	aagtttcttg	ccttctggag	tttttgatgg	tatgcctoca	2160
aatctaaaga	atctctcttt	ggccaaaaat	gggtctcaat	ctttcagttg	gaagaaactc	2220
cagtgtctaa	agaacctgga	aactttggac	ctcagccaca	accaactgac	cactgtccct	2280
gagagattat	ccaactgttc	cagaagcctc	agaatctga	ttcttaagaa	taatcaaatc	2340
aggagtctga	cgaagtattt	tctacaagat	gccttccagt	tgcgatatct	ggatctcagc	2400
tcaataaaaa	tccagatgat	ccaaaagacc	agcttcccag	aaaatgtcct	caacaatctg	2460
aagatgttgc	ttttgcatca	taatcggttt	ctgtgcacct	gtgatgctgt	gtggtttgtc	2520
tggtgggtta	accatacggg	ggtgactatt	ccttacctgg	ccacagatgt	gacttggtgtg	2580
gggccaggag	cacacaaggg	ccaaagtgtg	atctccctgg	atctgtacac	ctgtgagtta	2640
gatctgacta	acctgattct	gttctcaatt	tccatatctg	tatctctctt	tctcatgggtg	2700
atgatgacag	caagtcacct	ctatttctgg	gatgtgtggt	atatttacca	tttctgtaag	2760
gccaaagataa	aggggtatca	gcgtctaata	tcaccagact	gttgctatga	tgctttttatt	2820
gtgtatgaca	ctaaagaccc	agctgtgacc	gagtgggttt	tggtctgagct	ggtggccaaa	2880
ctggaagacc	caagagagaa	acattttaat	ttatgtctcg	aggaaaggga	ctggtttacca	2940
gggcagccag	ttctggaaaa	cctttcccag	agcatacagc	ttagcaaaaa	gacagtgttt	3000
gtgatgacag	acaagtatgc	aaagactgaa	aatttttaaga	tagcatttta	cttgteccat	3060
cagaggctca	tggtatgaaa	agttgatgtg	attatcttga	tatttcttga	gaagcccttt	3120
cagaagtcca	agttcctcca	gctccggaaa	aggctctgtg	ggagtctctgt	ccttgagtggt	3180
ccaacaaacc	cgcaagctca	cccatacttc	tggcagtgtc	taaagaacgc	cctggccaca	3240
gacaatcatg	tggtctatag	tcaggtgttc	aaggaaacgg	tctagccctt	ctttgcaaaa	3300

cacaactgcc tagtttacca aggagaggcc tggctgttta aattgttttc atatatatca 3360

caccaaaagc gtgttttgaa attcttcaag aaatgagatt gcccatattt caggggag 3418

<210> 34

<211> 1049

<212> PRT

<213> Homo sapiens

<400> 34

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
1 5 10 15

Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro

			260					265					270			
Cys	Lys	Asn	Asn	Ser	Pro	Leu	Gln	Ile	Pro	Val	Asn	Ala	Phe	Asp	Ala	
		275					280					285				
Leu	Thr	Glu	Leu	Lys	Val	Leu	Arg	Leu	His	Ser	Asn	Ser	Leu	Gln	His	
	290					295					300					
Val	Pro	Pro	Arg	Trp	Phe	Lys	Asn	Ile	Asn	Lys	Leu	Gln	Glu	Leu	Asp	
305					310					315					320	
Leu	Ser	Gln	Asn	Phe	Leu	Ala	Lys	Glu	Ile	Gly	Asp	Ala	Lys	Phe	Leu	
				325					330					335		
His	Phe	Leu	Pro	Ser	Leu	Ile	Gln	Leu	Asp	Leu	Ser	Phe	Asn	Phe	Glu	
			340					345					350			
Leu	Gln	Val	Tyr	Arg	Ala	Ser	Met	Asn	Leu	Ser	Gln	Ala	Phe	Ser	Ser	
		355					360					365				
Leu	Lys	Ser	Leu	Lys	Ile	Leu	Arg	Ile	Arg	Gly	Tyr	Val	Phe	Lys	Glu	
	370					375					380					
Leu	Lys	Ser	Phe	Asn	Leu	Ser	Pro	Leu	His	Asn	Leu	Gln	Asn	Leu	Glu	
385					390					395					400	
Val	Leu	Asp	Leu	Gly	Thr	Asn	Phe	Ile	Lys	Ile	Ala	Asn	Leu	Ser	Met	
				405					410					415		
Phe	Lys	Gln	Phe	Lys	Arg	Leu	Lys	Val	Ile	Asp	Leu	Ser	Val	Asn	Lys	
			420					425					430			
Ile	Ser	Pro	Ser	Gly	Asp	Ser	Ser	Glu	Val	Gly	Phe	Cys	Ser	Asn	Ala	
		435					440					445				
Arg	Thr	Ser	Val	Glu	Ser	Tyr	Glu	Pro	Gln	Val	Leu	Glu	Gln	Leu	His	
	450					455					460					
Tyr	Phe	Arg	Tyr	Asp	Lys	Tyr	Ala	Arg	Ser	Cys	Arg	Phe	Lys	Asn	Lys	
465					470					475					480	
Glu	Ala	Ser	Phe	Met	Ser	Val	Asn	Glu	Ser	Cys	Tyr	Lys	Tyr	Gly	Gln	
				485					490					495		
Thr	Leu	Asp	Leu	Ser	Lys	Asn	Ser	Ile	Phe	Phe	Val	Lys	Ser	Ser	Asp	
			500					505					510			
Phe	Gln	His	Leu	Ser	Phe	Leu	Lys	Cys	Leu	Asn	Leu	Ser	Gly	Asn	Leu	
		515					520					525				
Ile	Ser	Gln	Thr	Leu	Asn	Gly	Ser	Glu	Phe	Gln	Pro	Leu	Ala	Glu	Leu	
	530					535					540					
Arg	Tyr	Leu	Asp	Phe	Ser	Asn	Asn	Arg	Leu	Asp	Leu	Leu	His	Ser	Thr	
545					550					555					560	
Ala	Phe	Glu	Glu	Leu	His	Lys	Leu	Glu	Val	Leu	Asp	Ile	Ser	Ser	Asn	
				565					570					575		
Ser	His	Tyr	Phe	Gln	Ser	Glu	Gly	Ile	Thr	His	Met	Leu	Asn	Phe	Thr	
			580					585					590			
Lys	Asn	Leu	Lys	Val	Leu	Gln	Lys	Leu	Met	Met	Asn	Asp	Asn	Asp	Ile	

595				600				605							
Ser	Ser	Ser	Thr	Ser	Arg	Thr	Met	Glu	Ser	Glu	Ser	Leu	Arg	Thr	Leu
610						615						620			
Glu	Phe	Arg	Gly	Asn	His	Leu	Asp	Val	Leu	Trp	Arg	Glu	Gly	Asp	Asn
625					630					635					640
Arg	Tyr	Leu	Gln	Leu	Phe	Lys	Asn	Leu	Leu	Lys	Leu	Glu	Glu	Leu	Asp
				645					650						655
Ile	Ser	Lys	Asn	Ser	Leu	Ser	Phe	Leu	Pro	Ser	Gly	Val	Phe	Asp	Gly
			660						665					670	
Met	Pro	Pro	Asn	Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys
			675				680						685		
Ser	Phe	Ser	Trp	Lys	Lys	Leu	Gln	Cys	Leu	Lys	Asn	Leu	Glu	Thr	Leu
	690					695					700				
Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Thr	Val	Pro	Glu	Arg	Leu	Ser	Asn
705					710					715					720
Cys	Ser	Arg	Ser	Leu	Lys	Asn	Leu	Ile	Leu	Lys	Asn	Asn	Gln	Ile	Arg
				725					730					735	
Ser	Leu	Thr	Lys	Tyr	Phe	Leu	Gln	Asp	Ala	Phe	Gln	Leu	Arg	Tyr	Leu
			740						745					750	
Asp	Leu	Ser	Ser	Asn	Lys	Ile	Gln	Met	Ile	Gln	Lys	Thr	Ser	Phe	Pro
		755					760						765		
Glu	Asn	Val	Leu	Asn	Asn	Leu	Lys	Met	Leu	Leu	Leu	His	His	Asn	Arg
	770					775					780				
Phe	Leu	Cys	Thr	Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn	His
785					790					795					800
Thr	Glu	Val	Thr	Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val	Gly
				805					810					815	
Pro	Gly	Ala	His	Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr	Thr
			820				825						830		
Cys	Glu	Leu	Asp	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Leu	Ser	Ile	Ser
		835					840						845		
Val	Ser	Leu	Phe	Leu	Met	Val	Met	Met	Thr	Ala	Ser	His	Leu	Tyr	Phe
		850				855					860				
Trp	Asp	Val	Trp	Tyr	Ile	Tyr	His	Phe	Cys	Lys	Ala	Lys	Ile	Lys	Gly
865					870					875					880
Tyr	Gln	Arg	Leu	Ile	Ser	Pro	Asp	Cys	Cys	Tyr	Asp	Ala	Phe	Ile	Val
				885					890					895	
Tyr	Asp	Thr	Lys	Asp	Pro	Ala	Val	Thr	Glu	Trp	Val	Leu	Ala	Glu	Leu
			900						905				910		
Val	Ala	Lys	Leu	Glu	Asp	Pro	Arg	Glu	Lys	His	Phe	Asn	Leu	Cys	Leu
		915					920						925		
Glu	Glu	Arg	Asp	Trp	Leu	Pro	Gly	Gln	Pro	Val	Leu	Glu	Asn	Leu	Ser

930 935 940
 Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
 945 950 955 960
 Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
 965 970 975
 Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
 980 985 990
 Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
 995 1000 1005
 Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
 1010 1015 1020
 Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His
 1025 1030 1035
 Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
 1040 1045

<210> 35
 <211> 1049
 <212> PRT
 <213> Homo sapiens

<400> 35

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
 1 5 10 15
 Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
 20 25 30
 Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
 35 40 45
 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
 50 55 60
 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
 65 70 75 80
 Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
 85 90 95
 Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
 100 105 110
 Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
 115 120 125
 Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140
 Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160
 Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
 165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
 180 185 190
 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
 210 215 220
 Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
 225 230 235 240
 Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
 245 250 255
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
 260 265 270
 Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
 275 280 285
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
 290 295 300
 Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
 305 310 315 320
 Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
 340 345 350
 Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
 355 360 365
 Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
 370 375 380
 Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
 405 410 415
 Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
 420 425 430
 Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
 435 440 445
 Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
 450 455 460
 Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
 465 470 475 480
 Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
 485 490 495
 Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp

500										505					510					
Phe	Gln	His	Leu	Ser	Phe	Leu	Lys	Cys	Leu	Asn	Leu	Ser	Gly	Asn	Leu					
		515					520						525							
Ile	Ser	Gln	Thr	Leu	Asn	Gly	Ser	Glu	Phe	Gln	Pro	Leu	Ala	Glu	Leu					
		530				535					540									
Arg	Tyr	Leu	Asp	Phe	Ser	Asn	Asn	Arg	Leu	Asp	Leu	Leu	His	Ser	Thr					
	545				550					555					560					
Ala	Phe	Glu	Glu	Leu	His	Lys	Leu	Glu	Val	Leu	Asp	Ile	Ser	Ser	Asn					
				565					570					575						
Ser	His	Tyr	Phe	Gln	Ser	Glu	Gly	Ile	Thr	His	Met	Leu	Asn	Phe	Thr					
			580					585					590							
Lys	Asn	Leu	Lys	Val	Leu	Gln	Lys	Leu	Met	Met	Asn	Asp	Asn	Asp	Ile					
		595					600					605								
Ser	Ser	Ser	Thr	Ser	Arg	Thr	Met	Glu	Ser	Glu	Ser	Leu	Arg	Thr	Leu					
		610				615						620								
Glu	Phe	Arg	Gly	Asn	His	Leu	Asp	Val	Leu	Trp	Arg	Glu	Gly	Asp	Asn					
	625				630					635					640					
Arg	Tyr	Leu	Gln	Leu	Phe	Lys	Asn	Leu	Leu	Lys	Leu	Glu	Glu	Leu	Asp					
				645					650						655					
Ile	Ser	Lys	Asn	Ser	Leu	Ser	Phe	Leu	Pro	Ser	Gly	Val	Phe	Asp	Gly					
			660					665					670							
Met	Pro	Pro	Asn	Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys					
		675					680					685								
Ser	Phe	Ser	Trp	Lys	Lys	Leu	Gln	Cys	Leu	Lys	Asn	Leu	Glu	Thr	Leu					
		690				695					700									
Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Thr	Val	Pro	Glu	Arg	Leu	Ser	Asn					
	705				710					715					720					
Cys	Ser	Arg	Ser	His	Lys	Asn	Leu	Ile	Leu	Lys	Asn	Asn	Gln	Ile	Arg					
				725					730					735						
Ser	Pro	Thr	Lys	Tyr	Phe	Leu	Gln	Asp	Ala	Phe	Gln	Leu	Arg	Tyr	Leu					
			740					745					750							
Asp	Leu	Ser	Ser	Asn	Lys	Ile	Gln	Met	Ile	Gln	Lys	Thr	Ser	Phe	Pro					
		755					760					765								
Glu	Asn	Val	Leu	Asn	Asn	Leu	Lys	Met	Leu	Leu	Leu	His	His	Asn	Arg					
		770				775						780								
Phe	Leu	Cys	Thr	Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn	His					
	785				790					795					800					
Thr	Glu	Val	Thr	Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val	Gly					
				805					810					815						
Pro	Gly	Ala	His	Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr	Thr					
			820				825					830								
Cys	Glu	Leu	Asp	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Leu	Ser	Ile	Ser					

835	840	845
Val Ser Leu Phe Leu Met	Val Met Met Thr Ala Ser	His Leu Tyr Phe
850	855	860
Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly		
865	870	875 880
Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val		
885	890	895
Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu		
900	905	910
Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu		
915	920	925
Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser		
930	935	940
Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys		
945	950	955 960
Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln		
965	970	975
Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu		
980	985	990
Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys		
995	1000	1005
Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro		
1010	1015	1020
Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His		
1025	1030	1035
Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val		
1040	1045	

<210> 36
 <211> 1049
 <212> PRT
 <213> Homo sapiens

<400> 36

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe		
1	5	10 15
Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys		
20	25	30
Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile		
35	40	45
Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro		
50	55	60
Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile		
65	70	75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
 85 90 95
 Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
 100 105 110
 Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
 115 120 125
 Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140
 Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160
 Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
 165 170 175
 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
 180 185 190
 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
 210 215 220
 Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
 225 230 235 240
 Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
 245 250 255
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
 260 265 270
 Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
 275 280 285
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
 290 295 300
 Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
 305 310 315 320
 Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
 340 345 350
 Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
 355 360 365
 Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
 370 375 380
 Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met

Phe	Lys	Gln	Phe	Lys	Arg	Leu	Lys	Val	Ile	Asp	Leu	Ser	Val	Asn	Lys
			420					425					430		
Ile	Ser	Pro	Ser	Gly	Asp	Ser	Ser	Glu	Val	Gly	Phe	Cys	Ser	Asn	Ala
		435					440					445			
Arg	Thr	Ser	Val	Glu	Ser	Tyr	Glu	Pro	Gln	Val	Leu	Glu	Gln	Leu	His
	450					455					460				
Tyr	Phe	Arg	Tyr	Asp	Lys	Tyr	Ala	Arg	Ser	Cys	Arg	Phe	Lys	Asn	Lys
465					470					475					480
Glu	Ala	Ser	Phe	Met	Ser	Val	Asn	Glu	Ser	Cys	Tyr	Lys	Tyr	Gly	Gln
				485					490					495	
Thr	Leu	Asp	Leu	Ser	Lys	Asn	Ser	Ile	Phe	Phe	Val	Lys	Ser	Ser	Asp
			500					505					510		
Phe	Gln	His	Leu	Ser	Phe	Leu	Lys	Cys	Leu	Asn	Leu	Ser	Gly	Asn	Leu
		515					520					525			
Ile	Ser	Gln	Thr	Leu	Asn	Gly	Ser	Glu	Phe	Gln	Pro	Leu	Ala	Glu	Leu
	530					535					540				
Arg	Tyr	Leu	Asp	Phe	Ser	Asn	Asn	Arg	Leu	Asp	Leu	Leu	His	Ser	Thr
545					550					555					560
Ala	Phe	Glu	Glu	Leu	His	Lys	Leu	Glu	Val	Leu	Asp	Ile	Ser	Ser	Asn
				565					570					575	
Ser	His	Tyr	Phe	Gln	Ser	Glu	Gly	Ile	Thr	His	Met	Leu	Asn	Phe	Thr
			580					585					590		
Lys	Asn	Leu	Lys	Val	Leu	Gln	Lys	Leu	Met	Met	Asn	Asp	Asn	Asp	Ile
		595					600					605			
Ser	Ser	Ser	Thr	Ser	Arg	Thr	Met	Glu	Ser	Glu	Ser	Leu	Arg	Thr	Leu
	610					615					620				
Glu	Phe	Arg	Gly	Asn	His	Leu	Asp	Val	Leu	Trp	Arg	Glu	Gly	Asp	Asn
625					630					635					640
Arg	Tyr	Leu	Gln	Leu	Phe	Lys	Asn	Leu	Leu	Lys	Leu	Glu	Glu	Leu	Asp
				645					650					655	
Ile	Ser	Lys	Asn	Ser	Leu	Ser	Phe	Leu	Pro	Ser	Gly	Val	Phe	Asp	Gly
			660					665					670		
Met	Pro	Pro	Asn	Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys
		675					680					685			
Ser	Phe	Ser	Trp	Lys	Lys	Leu	Gln	Cys	Leu	Lys	Asn	Leu	Glu	Thr	Leu
	690					695					700				
Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Thr	Val	Pro	Glu	Arg	Leu	Ser	Asn
705					710					715					720
Cys	Ser	Arg	Ser	Leu	Lys	Asn	Leu	Ile	Leu	Lys	Asn	Asn	Gln	Ile	Arg
				725					730					735	
Ser	Leu	Thr	Lys	Tyr	Phe	Leu	Gln	Asp	Ala	Phe	Gln	Leu	Arg	Tyr	Leu

```

      740      745      750
Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro
      755      760      765

Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg
      770      775      780

Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
      785      790      795      800

Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
      805      810      815

Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
      820      825      830

Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser
      835      840      845

Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
      850      855      860

Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
      865      870      875      880

Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
      885      890      895

Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
      900      905      910

Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
      915      920      925

Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
      930      935      940

Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
      945      950      955      960

Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
      965      970      975

Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
      980      985      990

Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
      995      1000      1005

Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
      1010      1015      1020

Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His
      1025      1030      1035

Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
      1040      1045

```

<210> 37
 <211> 1049
 <212> PRT

<213> Homo sapiens

<400> 37

```

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
1           5           10           15

Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
          20           25           30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
          35           40           45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
          50           55           60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
65           70           75           80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
          85           90           95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
          100          105          110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
          115          120          125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
          130          135          140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145          150          155          160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
          165          170          175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
          180          185          190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
          195          200          205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
          210          215          220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225          230          235          240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
          245          250          255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
          260          265          270

Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
          275          280          285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
          290          295          300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
305          310          315          320

```

Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
 340 345 350
 Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
 355 360 365
 Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
 370 375 380
 Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
 405 410 415
 Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
 420 425 430
 Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
 435 440 445
 Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
 450 455 460
 Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
 465 470 475 480
 Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
 485 490 495
 Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp
 500 505 510
 Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
 515 520 525
 Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
 530 535 540
 Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
 545 550 555 560
 Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
 565 570 575
 Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
 580 585 590
 Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile
 595 600 605
 Ser Ser Ser Thr Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu
 610 615 620
 Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn
 625 630 635 640
 Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp

Ile	Ser	Lys	Asn	Ser	Leu	Ser	Phe	Leu	Pro	Ser	Gly	Val	Phe	Asp	Gly
			645					650						655	
			660					665						670	
Met	Pro	Pro	Asn	Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys
			675				680						685		
Ser	Phe	Ser	Trp	Lys	Lys	Leu	Gln	Cys	Leu	Lys	Asn	Leu	Glu	Thr	Leu
	690					695					700				
Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Thr	Val	Pro	Glu	Arg	Leu	Ser	Asn
705					710					715					720
Cys	Ser	Arg	Ser	Leu	Lys	Asn	Leu	Ile	Leu	Lys	Asn	Asn	Gln	Ile	Arg
				725				730						735	
Ser	Leu	Thr	Lys	Tyr	Phe	Leu	Gln	Asp	Ala	Phe	Gln	Leu	Arg	Tyr	Leu
			740					745					750		
Asp	Leu	Ser	Ser	Asn	Lys	Ile	Gln	Met	Ile	Gln	Lys	Thr	Ser	Phe	Pro
		755					760					765			
Glu	Asn	Val	Leu	Asn	Asn	Leu	Lys	Met	Leu	Leu	Leu	His	His	Asn	Arg
	770					775						780			
Phe	Leu	Cys	Thr	Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn	His
785					790					795					800
Thr	Glu	Val	Thr	Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val	Gly
				805					810					815	
Pro	Gly	Ala	His	Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr	Thr
			820					825					830		
Cys	Glu	Leu	Asp	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Leu	Ser	Ile	Ser
		835					840						845		
Val	Ser	Leu	Phe	Leu	Met	Val	Met	Met	Thr	Ala	Ser	His	Leu	Tyr	Phe
	850					855					860				
Trp	Asp	Val	Trp	Tyr	Ile	Tyr	His	Phe	Cys	Lys	Ala	Lys	Ile	Lys	Gly
865					870					875					880
Tyr	Gln	Arg	Leu	Ile	Ser	Pro	Asp	Cys	Cys	Tyr	Asp	Ala	Phe	Ile	Val
			885					890						895	
Tyr	Asp	Thr	Lys	Asp	Pro	Ala	Val	Thr	Glu	Trp	Val	Leu	Ala	Glu	Leu
			900					905					910		
Val	Ala	Lys	Leu	Glu	Asp	Pro	Arg	Glu	Lys	His	Phe	Asn	Leu	Cys	Leu
		915						920					925		
Glu	Glu	Arg	Asp	Trp	Leu	Pro	Gly	Gln	Pro	Val	Leu	Glu	Asn	Leu	Ser
	930					935					940				
Gln	Ser	Ile	Gln	Leu	Ser	Lys	Lys	Thr	Val	Phe	Val	Met	Thr	Asp	Lys
945					950					955					960
Tyr	Ala	Lys	Thr	Glu	Asn	Phe	Lys	Ile	Ala	Phe	Tyr	Leu	Ser	His	Gln
			965					970						975	
Arg	Leu	Met	Asp	Glu	Lys	Val	Asp	Val	Ile	Ile	Leu	Ile	Phe	Leu	Glu

[illegible]

<210>	38
<211>	3243
<212>	DNA
<213>	murine

<400>	38						
attctcctcc	accgacctc	ttgattccat	tttgaaagaa	aactgaaaat	ggtgttttcg		60
atgtggacac	ggaagagaca	aattttgatc	tttttaaata	tgctcttagt	ttctagagtc		120
tttgggtttc	gatggtttcc	taaaactcta	ccttgtgaag	ttaaagtaaa	tatcccagag		180
gcccattgtga	tcgtggactg	cacagacaag	catttgacag	aaatccctga	gggcattccc		240
actaacacca	ccaatcttac	ccttaccatc	aaccacatac	caagcatctc	tccagattcc		300
ttccgtaggc	tgaaccatct	ggaagaaatc	gatttaagat	gcaattgtgt	acctgttcta		360
ctggggtcca	aagccaatgt	gtgtaccaag	aggctgcaga	ttagacctgg	aagctttagt		420
ggactctctg	acttaaaagc	cctttacctg	gatggaaacc	aacttctgga	gataccacag		480
gatctgccat	ccagcttaca	tcttctgagc	cttgaggcta	acaacatctt	ctccatcacg		540
aaggagaatc	taacagaact	ggtcaacatt	gaaacactct	acctgggtca	aaactgttat		600
tatcgaaatc	cttgcaatgt	ttcctattct	attgaaaaag	atgctttcct	agttatgaga		660
aatttgaagg	ttctctcact	aaaagataac	aatgtcacag	ctgtccccac	cactttgcca		720
cctaatttac	tagagctcta	tctttataac	aatatcatta	agaaaatcca	agaaaatgat		780
tttaataacc	tcaatgagtt	gcaagttctt	gacctaatgt	gaaattgccc	tcgatgttat		840
aatgtcccat	atccgtgtac	accgtgtgaa	aataattccc	ccttacagat	ccatgacaat		900
gctttcaatt	cattgacaga	attaaaagtt	ttacgtttac	acagtaattc	tcttcagcat		960
gtgcccccaa	catggtttta	aaacatgaga	aacctccagg	aactagacct	ctcccaaaac		1020
tacttgacca	gagaaattga	ggaggccaaa	tttttgcat	ttcttcccaa	ccttgttgag		1080
ttggattttt	ctttcaatta	tgagctgcag	gtctaccatg	catctataac	tttaccacat		1140
tcactctctt	cattggaaaa	cttgaaaatt	ctgcgtgtca	aggggtatgt	ctttaaagag		1200
ctgaaaaaact	ccagtctttc	tgtattgcac	aagcttccca	ggctggaagt	tcttgacctt		1260

ggcactaact tcataaaaat tgctgacctc aacatattca aacattttga aaacctcaaa	1320
ctcatagacc tttcagtgaa taagatatct ccttcagaag agtcaagaga agttggcttt	1380
tgccctaattg ctcaaacttc tgtagaccgt catgggcccc aggtccttga ggccttacac	1440
tatttccgat acgatgaata tgcacggagc tgcaggttca aaaacaaaga gccaccttct	1500
ttcttgctt tgatgcaga ctgccacata tatgggcaga ccttagactt aagtagaaat	1560
aacatatttt ttattaaacc ttctgatttt cagcatcttt cattcctcaa atgcctcaac	1620
ttatcaggaa acaccattgg ccaaactctt aatggcagtg aactctggcc gttgagagag	1680
ttgcggtact tagacttctc caacaaccgg cttgatttac tctactcaac agcctttgaa	1740
gagctccaga gtcttgaagt tctggatcta agtagtaaca gccactattt tcaagcagaa	1800
ggaattactc acatgctaaa ctttaccaag aaattacggc ttctggacaa actcatgatg	1860
aatgataatg acatctctac ttcgccagc aggaccatgg aaagtgactc tcttcgaatt	1920
ctggagttca gaggcaacca tttagatgtt ctatggagag cgggtgataa cagatacttg	1980
gacttcttca agaatttggt caatttagag gtattagata tctccagaaa ttccctgaat	2040
tccttgctc ctgaggtttt tgagggtatg ccgccaaatc taaagaatct ctcttgggc	2100
aaaaatgggc tcaaactctt cttttgggac agactccagt tactgaagca tttggaaatt	2160
ttggacctca gccataacca gctgacaaaa gtacctgaga gattggccaa ctgttccaaa	2220
agtctcacia cactgattct taagcataat caaatcaggc aattgacaaa atattttcta	2280
gaagatgctt tgcaattgct ctatctagac atcagttcaa ataaaatcca ggtcattcag	2340
aagactagct tcccagaaaa tgcctcaac aatctggaga tggttggtttt acatcacaat	2400
cgctttcttt gcaactgtga tgctgtgtgg tttgtctggt gggttaacca tacagatgtt	2460
actattccat acctggccac tgatgtgact tgtgtaggtc caggagcaca caaagggtcaa	2520
agtgtcatat cccttgatct gtatacgtgt gagttagatc tcacaaacct gattctgttc	2580
tcagtttcca tatcatcagt cctctttctt atggtagtta tgacaacaag tcacctcttt	2640
ttctgggata tgtggtacat ttattatttt tggaaagcaa agataaagggt gtatcagcat	2700
ctgcaatcca tggagtcttg ttatgatgct tttatttgtt atgacactaa aaactcagct	2760
gtgacagaat gggttttgca ggagctgggt gcaaaattgg aagatccaag agaaaaacac	2820
ttcaatttgt gtctagaaga aagagactgg ctaccaggac agccagttct agaaaacctt	2880
tcccagagca tacagctcag caaaaagaca gtgtttgtga tgacacagaa atatgctaag	2940
actgagagtt ttaagatggc attttatttg tctcatcaga ggctcctgga tgaaaaagtg	3000
gatgtgatta tcttgatatt cttggaaaag cctcttcaga agtctaagtt tcttcagctc	3060
aggaagagac tctgcaggag ctctgtcctt gagtggcctg caaatccaca ggctcaccca	3120
tacttctggc agtgctgaa aaatgccctg accacagaca atcatgtggc ttatagtcaa	3180

atgttcaagg aaacagtcta gctctctgaa gaatgtcacc acctaggaca tgccttgaat 3240
cga 3243

<210> 39
<211> 3747
<212> DNA
<213> murine

<400> 39
gagctcaaag gctctgagag tctcggtttt ctgttgcctt ctctctgtct cagaggactc 60
catctataga accactctat gccttcaaga aagatgtcct tggctccctt ctcaggatga 120
tcctggccta tctctgactc tcttctctc caccagacct cttgattcca ttttgaaaga 180
aaactgaaaa tgggtgtttt gatgtggaca cggaagagac aaattttgat ctttttaaata 240
atgctcttag tttctagagt ctttgggttt cgatgggttt ctaaaactct accttgtgaa 300
gttaaagtaa atatcccaga ggcccatgtg atcgtggact gcacagacaa gcatttgaca 360
gaaatccctg agggcattcc cactaacacc accaatctta cccttaccat caaccacata 420
ccaagcatct ctccagattc cttccgtagg ctgaaccatc tggagaaat cgatttaaga 480
tgcaattgtg tacctgttct actggggtcc aaagccaatg tgtgtaccaa gaggtgcag 540
attagacctg gaagcttttag tggactctct gacttaaaag ccctttacct ggatggaaac 600
caacttctgg agataccaca ggatctgcca tccagcttac atcttctgag ccttgaggct 660
aacaacatct tctccatcac gaaggagaat ctaacagaac tgggtcaacat tgaaacactc 720
tacctgggtc aaaactgtta ttatcgaaat ctttgcaatg tttcctattc tattgaaaaa 780
gatgctttcc tagttatgag aaatttgaag gttctctcac taaaagataa caatgtcaca 840
gctgtcccca ccactttgcc acctaattha ctagagctct atctttataa caatatcatt 900
aagaaaatcc aagaaaatga ttttaataac ctcaatgagt tgcaagtctc tgacctaatg 960
ggaaattgcc ctgatgtta taatgtccca tatccgtgta caccgtgtga aaataattcc 1020
cccttacaga tccatgacaa tgctttcaat tcattgacag aattaaaagt tttacgttta 1080
cacagtaatt ctcttcagca tgtgccccca acatgggtta aaaacatgag aaacctccag 1140
gaactagacc tctcccaaaa ctacttggtc agagaaattg aggaggccaa atttttgcat 1200
tttcttccca accttgttga gttggatttt tctttcaatt atgagctgca ggtctaccat 1260
gcatctataa ctttaccaca ttcactctct tcattggaaa acttgaaaat tctgcgtgtc 1320
aaggggtatg tctttaaaga gctgaaaaac tccagtcttt ctgtattgca caagcttccc 1380
aggctggaag ttcttgacct tggcactaac ttcataaaaa ttgctgacct caacatatct 1440
aaacattttg aaaacctcaa actcatagac ctttcagtga ataagatatc tccttcagaa 1500

gagtcaagag aagttggctt ttgtccta	gctcaaactt ctgtagaccg tcatgggccc	1560
caggtccttg aggccttaca ctatttccga	tacgatgaat atgcacggag ctgcaggttc	1620
aaaaacaaag agccaccttc tttcttgcc	ttgaatgcag actgccacat atatgggcag	1680
accttagact taagtagaaa taacatattt	tttattaaac cttctgattt tcagcatctt	1740
tcattcctca aatgcctcaa cttatcagga	aacaccattg gccaaactct taatggcagt	1800
gaactctggc cgttgagaga gttgcggtac	ttagacttct ccaacaaccg gcttgattta	1860
ctctactcaa cagcctttga agagctccag	agtcttgaag ttctggatct aagtagtaac	1920
agccactatt ttcaagcaga aggaattact	cacatgctaa actttacca gaaattacgg	1980
cttctggaca aactcatgat gaatgataat	gacatctcta cttcggccag caggaccatg	2040
gaaagtgact ctcttcgaat tctggagttc	agaggcaacc atttagatgt tctatggaga	2100
gccggtgata acagatactt ggacttcttc	aagaatttgt tcaatttaga ggtattagat	2160
atctccagaa attccctgaa ttccttgcc	cctgaggttt ttgaggggat gccgccaaat	2220
ctaaagaatc tctccttggc caaaaatggg	ctcaaactct tcttttggga cagactccag	2280
ttactgaagc atttggaat tttggacctc	agccataacc agctgacaaa agtacctgag	2340
agattggcca actgttccaa aagtctcaca	acactgattc ttaagcataa tcaaactcag	2400
caattgacaa aatattttct agaagatgct	ttgcaattgc gctatctaga catcagttca	2460
aataaaatcc aggtcattca gaagactagc	ttcccagaaa atgtcctcaa caatctggag	2520
atgttggttt tacatcacia tcgctttctt	tgcaactgtg atgctgtgtg gtttgtctgg	2580
tgggttaacc atacagatgt tactattcca	tacctggcca ctgatgtgac ttgtgtaggt	2640
ccaggagcac acaaaggcca aagtgtcata	tccttgatc tgtatacgtg tgagttagat	2700
ctcacaaacc tgattctgtt ctcagtttcc	atatcatcag tcctctttct tatggtagtt	2760
atgacaacaa gtcacctctt tttctgggat	atgtggtaca tttattattt ttggaaagca	2820
aagataaagg ggtatcagca tctgcaatcc	atggagtctt gttatgatgc ttttattgtg	2880
tatgacacta aaaactcagc tgtgacagaa	tgggttttgc aggagctggt ggcaaaattg	2940
gaagatccaa gagaaaaaca cttcaatttg	tgtctagaag aaagagactg gctaccagga	3000
cagccagttc tagaaaacct ttcccagagc	atacagctca gcaaaaagac agtgtttgtg	3060
atgacacaga aatatgctaa gactgagagt	tttaagatgg cattttattt gtctcatcag	3120
aggctcctgg atgaaaaagt ggatgtgatt	atcttgatat tcttggaata gcctcttcag	3180
aagtctaagt ttcttcagct caggaagaga	ctctgcagga gctctgtcct tgagtggcct	3240
gcaaatccac aggtccaccc atactctctg	cagtgcctga aaaatgccct gaccacagac	3300
aatcatgtgg cttatagtca aatgttcaag	gaaacagtct agctctctga agaatgtcac	3360
cacctaggac atgccttggg acctgaagtt	ttcataaagg tttccataaa tgaaggtctg	3420

aatttttctcct aacagttgtc atggctcaga ttggtgggaa atcatcaata tatggctaag 3480
aaattaagaa ggggagactg atagaagata atttctttct tcatgtgcca tgctcagtta 3540
aatattttccc ctagctcaaa tctgaaaaac tgtgcctagg agacaacaca aggctttgat 3600
ttatctgcat acaattgata agagccacac atctgccctg aagaagtact agtagtttta 3660
gtagtagggg aaaaattaca caagctttct ctctctctga tactgaactg taccagagtt 3720
caatgaaata aaagcccaga gaacttc 3747

<210> 40
<211> 3449
<212> DNA
<213> murine

<400> 40
gcgagtctcg gttttctggt gccttctctc tgtctcagag gactccatct atagaaccac 60
tctatgcctt caagaaagat gtccttggct cccttctcag gatgatcctg gcctatctct 120
gactctcttc tcctccacca gacctcttga ttccattttg aaagaaaact gaaaatgggtg 180
ttttcgatgt ggacacggaa gagacaaatt ttgatctttt taaatatgct cttagtttct 240
agagtctttg ggtttcgatg gtttcctaaa actctacctt gtgaagttaa agtaaatact 300
ccagaggccc atgtgatcgt ggactgcaca gacaagcatt tgacagaaat ccctgagggc 360
attcccacta acaccaccaa tcttaccctt accatcaacc acataccaag catctctcca 420
gattcccttc gtaggctgaa ccatctggaa gaaatcgatt taagatgcaa ttgtgtacct 480
gttctactgg ggtccaaagc caatgtgtgt accaagaggc tgcagattag acctggaagc 540
tttagtggac tctctgactt aaaagccctt tacctggatg gaaaccaact tctggagata 600
ccacaggatc tgccatccag cttacatctt ctgagccttg aggctaacaa catcttctcc 660
atcacgaagg agaactaac agaactggtc aacattgaaa cactctacct gggtcaaac 720
tgttattatc gaaatccttg caatgtttcc tattctattg aaaaagatgc tttcctagtt 780
atgagaaatt tgaaggttct ctactaaaa gataacaatg tcacagctgt cccaccact 840
ttgccaccta atttactaga gctctatctt tataacaata tcattaagaa aatccaagaa 900
aatgatttta ataacctcaa tgagttgcaa gttcttgacc taagtggaaa ttgccctcga 960
tgttataatg tcccatatcc gtgtacaccg tgtgaaaata attccccctt acagatccat 1020
gacaatgctt tcaattcatt gacagaatta aaagttttac gtttacacag taattctctt 1080
cagcatgtgc ccccaacatg gtttaaaaac atgagaaacc tccaggaact agacctctcc 1140
caaaactact tggccagaga aattgaggag gccaaatatt tgcattttct tcccaacctt 1200
gttgagttgg atttttcttt caattatgag ctgcaggctt accatgcac tataacttta 1260

ccacattcac tctcttcatt ggaaaacttg aaaattctgc gtgtcaaggg gtatgtcttt	1320
aaagagctga aaaactccag tctttctgta ttgcacaagc ttcccaggct ggaagttctt	1380
gaccttggca ctaacttcat aaaaattgct gacctcaaca tattcaaaca ttttgaaaac	1440
ctcaaactca tagacctttc agtgaataag atatctcctt cagaagagtc aagagaagtt	1500
ggcttttgtc ctaatgctca aacttctgta gaccgtcatg ggccccaggc ccttgaggcc	1560
ttacactatt tccgatacga tgaatatgca cggagctgca ggttcaaaaa caaagagcca	1620
ccttctttct tgcctttgaa tgcagactgc cacatatatg ggagacctt agacttaagt	1680
agaaataaca ttttttttat taaaccttct gattttcagc atctttcatt cctcaaagtc	1740
ctcaacttat caggaaacac cattggccaa actcttaatg gcagtgaact ctggccgttg	1800
agagagttgc ggtacttaga cttctccaac aaccggcttg atttactcta ctcaacagcc	1860
tttgaagagc tccagagtct tgaagttctg gatctaagta gtaacagcca ctattttcaa	1920
gcagaaggaa ttactcacat gctaaacttt accaagaaat tacggcttct ggacaaactc	1980
atgatgaatg ataatgacat ctctacttcg gccagcagga ccatggaaag tgactctctt	2040
cgaattcttg agttcagagg caaccattta gatgttctat ggagagccgg tgataacaga	2100
tacttggact tcttcaagaa tttgttcaat ttagaggat tagatatctc cagaaattcc	2160
ctgaattcct tgcctcctga ggtttttgag ggtatgccgc caaatctaaa gaatctctcc	2220
ttggccaaaa atgggctcaa atctttcttt tgggacagac tccagttact gaagcatttg	2280
gaaatttttg acctcagcca taaccagctg acaaaagtac ctgagagatt ggccaactgt	2340
tccaaaagtc tcacaacact gattcttaag cataatcaaa tcaggcaatt gacaaaatat	2400
tttctagaag atgctttgca attgcgctat ctagacatca gttcaaataa aatccaggtc	2460
attcagaaga ctagcttccc agaaaatgtc ctcaacaatc tggagatgtt ggttttacat	2520
cacaatcgct ttctttgcaa ctgtgatgct gtgtggtttg tctgggtggg taaccataca	2580
gatgttacta ttccatacct ggccactgat gtgacttggt taggtccagg agcacacaaa	2640
ggtcaaagtg tcatatccct tgatctgtat acgtgtgagt tagatctcac aaacctgatt	2700
ctgttctcag ttccatatac atcagtcctc tttcttatgg tagttatgac aacaagtcac	2760
ctctttttct gggatatgtg gtacatttat ttttttggga aagcaaagat aaaggggtat	2820
cagcatctgc aatccatgga gtcttggtat gatgctttta ttgtgtatga cactaaaaac	2880
tcagctgtga cagaatgggt tttgcaggag ctggtggcaa aattggaaga tccaagagaa	2940
aaacacttca atttgtgtct agaagaaaga gactggctac caggacagcc agttctagaa	3000
aacctttccc agagcataca gctcagcaaa aagacagtgt ttgtgatgac acagaaatat	3060
gctaagactg agagttttta gatggcattt ttttgtctc atcagaggct cctggatgaa	3120
aaagtggatg tgattatctt gatattcttg gaaaagcctc ttcagaagtc taagtttctt	3180

cagctcagga agagactctg caggagctct gtccttgagt ggcttgcaaa tccacaggct 3240
 caccataact tctggcagtg cctgaaaaat gccctgacca cagacaatca tgtggcttat 3300
 agtcaaatgt tcaaggaaac agtctagctc tctgaagaat gtcaccacct aggacatgcc 3360
 ttggtacctg aagttttcat aaaggtttcc ataaatgaag gtctgaattt ttcctaacag 3420
 ttgtcatggc tcagattggg gggaaatca 3449

<210> 41
 <211> 1050
 <212> PRT
 <213> murine
 <400> 41

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
 1 5 10 15
 Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
 20 25 30
 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
 35 40 45
 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
 50 55 60
 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
 65 70 75 80
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
 85 90 95
 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
 100 105 110
 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
 115 120 125
 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140
 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160
 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
 165 170 175
 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
 180 185 190
 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
 210 215 220
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile

225	230										235					240		
Gln	Glu	Asn	Asp	Phe	Asn	Asn	Leu	Asn	Glu	Leu	Gln	Val	Leu	Asp	Leu			
				245					250						255			
Ser	Gly	Asn	Cys	Pro	Arg	Cys	Tyr	Asn	Val	Pro	Tyr	Pro	Cys	Thr	Pro			
				260					265						270			
Cys	Glu	Asn	Asn	Ser	Pro	Leu	Gln	Ile	His	Asp	Asn	Ala	Phe	Asn	Ser			
				275					280						285			
Leu	Thr	Glu	Leu	Lys	Val	Leu	Arg	Leu	His	Ser	Asn	Ser	Leu	Gln	His			
				290					295						300			
Val	Pro	Pro	Thr	Trp	Phe	Lys	Asn	Met	Arg	Asn	Leu	Gln	Glu	Leu	Asp			
				305					310						320			
Leu	Ser	Gln	Asn	Tyr	Leu	Ala	Arg	Glu	Ile	Glu	Glu	Ala	Lys	Phe	Leu			
				325					330						335			
His	Phe	Leu	Pro	Asn	Leu	Val	Glu	Leu	Asp	Phe	Ser	Phe	Asn	Tyr	Glu			
				340					345						350			
Leu	Gln	Val	Tyr	His	Ala	Ser	Ile	Thr	Leu	Pro	His	Ser	Leu	Ser	Ser			
				355					360						365			
Leu	Glu	Asn	Leu	Lys	Ile	Leu	Arg	Val	Lys	Gly	Tyr	Val	Phe	Lys	Glu			
				370					375						380			
Leu	Lys	Asn	Ser	Ser	Leu	Ser	Val	Leu	His	Lys	Leu	Pro	Arg	Leu	Glu			
				385					390						400			
Val	Leu	Asp	Leu	Gly	Thr	Asn	Phe	Ile	Lys	Ile	Ala	Asp	Leu	Asn	Ile			
				405					410						415			
Phe	Lys	His	Phe	Glu	Asn	Leu	Lys	Leu	Ile	Asp	Leu	Ser	Val	Asn	Lys			
				420					425						430			
Ile	Ser	Pro	Ser	Glu	Glu	Ser	Arg	Glu	Val	Gly	Phe	Cys	Pro	Asn	Ala			
				435					440						445			
Gln	Thr	Ser	Val	Asp	Arg	His	Gly	Pro	Gln	Val	Leu	Glu	Ala	Leu	His			
				450					455						460			
Tyr	Phe	Arg	Tyr	Asp	Glu	Tyr	Ala	Arg	Ser	Cys	Arg	Phe	Lys	Asn	Lys			
				465					470						480			
Glu	Pro	Pro	Ser	Phe	Leu	Pro	Leu	Asn	Ala	Asp	Cys	His	Ile	Tyr	Gly			
				485					490						495			
Gln	Thr	Leu	Asp	Leu	Ser	Arg	Asn	Asn	Ile	Phe	Phe	Ile	Lys	Pro	Ser			
				500					505						510			
Asp	Phe	Gln	His	Leu	Ser	Phe	Leu	Lys	Cys	Leu	Asn	Leu	Ser	Gly	Asn			
				515					520						525			
Thr	Ile	Gly	Gln	Thr	Leu	Asn	Gly	Ser	Glu	Leu	Trp	Pro	Leu	Arg	Glu			
				530					535						540			
Leu	Arg	Tyr	Leu	Asp	Phe	Ser	Asn	Asn	Arg	Leu	Asp	Leu	Leu	Tyr	Ser			
				545					550						560			
Thr	Ala	Phe	Glu	Glu	Leu	Gln	Ser	Leu	Glu	Val	Leu	Asp	Leu	Ser	Ser			

565 570 575
 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
 580 585 590
 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
 595 600 605
 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
 610 615 620
 Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
 625 630 635 640
 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
 645 650 655
 Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
 660 665 670
 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
 675 680 685
 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
 690 695 700
 Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala
 705 710 715 720
 Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
 725 730 735
 Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
 740 745 750
 Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
 755 760 765
 Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
 770 775 780
 Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
 785 790 795 800
 His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val
 805 810 815
 Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
 820 825 830
 Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
 835 840 845
 Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe
 850 855 860
 Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
 865 870 875 880
 Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
 885 890 895
 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu

900 905 910
 Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
 915 920 925
 Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
 930 935 940
 Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
 945 950 955 960
 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
 965 970 975
 Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
 980 985 990
 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
 995 1000 1005
 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
 1010 1015 1020
 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
 1025 1030 1035
 His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
 1040 1045 1050

<210> 42
 <211> 1050
 <212> PRT
 <213> murine

<400> 42

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
 1 5 10 15
 Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
 20 25 30
 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
 35 40 45
 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
 50 55 60
 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
 65 70 75 80
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
 85 90 95
 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
 100 105 110
 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
 115 120 125
 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140

Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160
 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
 165 170 175
 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
 180 185 190
 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
 210 215 220
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
 225 230 235 240
 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
 245 250 255
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
 260 265 270
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
 275 280 285
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
 290 295 300
 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
 305 310 315 320
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
 340 345 350
 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
 355 360 365
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu
 370 375 380
 Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
 405 410 415
 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
 420 425 430
 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
 435 440 445
 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
 450 455 460
 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys

465 470 475 480
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
 485 490 495

 Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
 500 505 510

 Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
 515 520 525

 Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
 530 535 540

 Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
 545 550 555 560

 Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
 565 570 575

 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
 580 585 590

 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
 595 600 605

 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
 610 615 620

 Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
 625 630 635 640

 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
 645 650 655

 Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
 660 665 670

 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
 675 680 685

 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
 690 695 700

 Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala
 705 710 715 720

 Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
 725 730 735

 Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
 740 745 750

 Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
 755 760 765

 Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
 770 775 780

 Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
 785 790 795 800

 His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val

Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
 805 810 815
 820 825 830
 Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
 835 840 845
 Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe
 850 855 860
 Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
 865 870 875 880
 Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
 885 890 895
 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu
 900 905 910
 Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
 915 920 925
 Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
 930 935 940
 Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
 945 950 955 960
 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
 965 970 975
 Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
 980 985 990
 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
 995 1000 1005
 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
 1010 1015 1020
 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
 1025 1030 1035
 His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
 1040 1045 1050

<210> 43
 <211> 1050
 <212> PRT
 <213> murine

<400> 43

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
 1 5 10 15
 Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
 20 25 30
 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
 35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
 50 55 60
 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
 65 70 75 80
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
 85 90 95
 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
 100 105 110
 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
 115 120 125
 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140
 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160
 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
 165 170 175
 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
 180 185 190
 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
 210 215 220
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
 225 230 235 240
 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
 245 250 255
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
 260 265 270
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
 275 280 285
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
 290 295 300
 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
 305 310 315 320
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
 340 345 350
 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
 355 360 365
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu

370 375 380
 Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
 405 410 415
 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
 420 425 430
 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
 435 440 445
 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
 450 455 460
 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
 465 470 475 480
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
 485 490 495
 Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
 500 505 510
 Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
 515 520 525
 Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
 530 535 540
 Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
 545 550 555 560
 Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
 565 570 575
 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
 580 585 590
 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
 595 600 605
 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
 610 615 620
 Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
 625 630 635 640
 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
 645 650 655
 Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
 660 665 670
 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
 675 680 685
 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
 690 695 700
 Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala

705	710	715	720
Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile 725 730 735			
Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr 740 745 750			
Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe 755 760 765			
Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn 770 775 780			
Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn 785 790 795 800			
His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val 805 810 815			
Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr 820 825 830			
Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile 835 840 845			
Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe 850 855 860			
Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys 865 870 875 880			
Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile 885 890 895			
Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu 900 905 910			
Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys 915 920 925			
Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu 930 935 940			
Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln 945 950 955 960			
Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His 965 970 975			
Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu 980 985 990			
Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu 995 1000 1005			
Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His 1010 1015 1020			
Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn 1025 1030 1035			
His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val			

1040 1045 1050
 <210> 44
 <211> 1050
 <212> PRT
 <213> murine
 <400> 44
 Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
 1 5 10 15
 Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
 20 25 30
 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
 35 40 45
 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
 50 55 60
 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
 65 70 75 80
 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
 85 90 95
 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
 100 105 110
 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
 115 120 125
 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140
 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160
 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
 165 170 175
 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
 180 185 190
 Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
 210 215 220
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
 225 230 235 240
 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
 245 250 255
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
 260 265 270
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
 275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
 290 295 300
 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
 305 310 315 320
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
 340 345 350
 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
 355 360 365
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu
 370 375 380
 Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
 405 410 415
 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
 420 425 430
 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
 435 440 445
 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
 450 455 460
 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
 465 470 475 480
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
 485 490 495
 Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
 500 505 510
 Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
 515 520 525
 Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
 530 535 540
 Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
 545 550 555 560
 Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
 565 570 575
 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
 580 585 590
 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
 595 600 605
 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile

610	615	620
Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp		
625	630	635
Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu		
645	650	655
Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu		
660	665	670
Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu		
675	680	685
Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile		
690	695	700
Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala		
705	710	715
Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile		
725	730	735
Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr		
740	745	750
Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe		
755	760	765
Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn		
770	775	780
Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn		
785	790	795
His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val		
805	810	815
Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr		
820	825	830
Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile		
835	840	845
Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe		
850	855	860
Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys		
865	870	875
Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile		
885	890	895
Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu		
900	905	910
Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys		
915	920	925
Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu		
930	935	940
Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln		

945 950 955 960
 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
 965 970 975

 Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
 980 985 990

 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
 995 1000 1005

 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
 1010 1015 1020

 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
 1025 1030 1035

 His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
 1040 1045 1050

<210> 45
 <211> 1050
 <212> PRT
 <213> murine

<400> 45

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
 1 5 10 15

 Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
 20 25 30

 Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
 35 40 45

 Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
 50 55 60

 Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
 65 70 75 80

 Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
 85 90 95

 Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
 100 105 110

 Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
 115 120 125

 Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140

 Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160

 Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
 165 170 175

 Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
 180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
 195 200 205
 Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
 210 215 220
 Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
 225 230 235 240
 Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
 245 250 255
 Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
 260 265 270
 Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
 275 280 285
 Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
 290 295 300
 Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
 305 310 315 320
 Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
 325 330 335
 His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
 340 345 350
 Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
 355 360 365
 Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu
 370 375 380
 Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
 385 390 395 400
 Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
 405 410 415
 Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
 420 425 430
 Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
 435 440 445
 Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
 450 455 460
 Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
 465 470 475 480
 Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
 485 490 495
 Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
 500 505 510
 Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn

515 520 525
 Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
 530 535 540
 Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
 545 550 555 560
 Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
 565 570 575
 Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
 580 585 590
 Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
 595 600 605
 Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
 610 615 620
 Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
 625 630 635 640
 Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
 645 650 655
 Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
 660 665 670
 Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
 675 680 685
 Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
 690 695 700
 Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala
 705 710 715 720
 Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
 725 730 735
 Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
 740 745 750
 Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
 755 760 765
 Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
 770 775 780
 Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
 785 790 795 800
 His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val
 805 810 815
 Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
 820 825 830
 Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
 835 840 845
 Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe

850 855 860
 Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
 865 870 875 880
 Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
 885 890 895
 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu
 900 905 910
 Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
 915 920 925
 Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
 930 935 940
 Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
 945 950 955 960
 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
 965 970 975
 Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
 980 985 990
 Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
 995 1000 1005
 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
 1010 1015 1020
 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
 1025 1030 1035
 His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
 1040 1045 1050

<210> 46

<211> 3311

<212> DNA

<213> Homo sapiens

<400> 46

ttctgcgctg ctgcaagtta cggaatgaaa aattagaaca acagaaacat ggaaaacatg 60
 ttccttcagt cgtcaatgct gacctgcatt ttctgctaa tatctgggtc ctgtgagtta 120
 tgcgccgaag aaaatttttc tagaagctat ccttgtgatg agaaaaagca aaatgactca 180
 gttattgcag agtgcagcaa tcgtcgacta caggaagttc cccaaacggt gggcaaatat 240
 gtgacagaac tagacctgtc tgataatttc atcacacaca taacgaatga atcattttcaa 300
 gggctgcaaa atctcactaa aataaatcta aaccacaacc ccaatgtaca gcaccagaac 360
 ggaaatcccg gtatacaatc aaatggcttg aatatcacag acggggcatt cctcaacctta 420
 aaaaacctaa gggagttact gcttgaagac aaccagttac cccaaatacc ctctggtttg 480
 ccagagtctt tgacagaact tagtctaatt caaaacaata tataacaacat aactaaagag 540

ggcatttcaa gacttataaa cttgaaaaat ctctatttgg cctggaactg ctatttttaac	600
aaagtttgcg agaaaactaa catagaagat ggagttattg aaacgctgac aaatttggag	660
ttgctatcac tatctttcaa ttctctttca cacgtgccac ccaaactgcc aagctcccta	720
cgcaaacttt ttctgagcaa caccagatc aaatacatta gtgaagaaga tttcaagggg	780
ttgataaatt taacattact agatttaagc gggaactgtc cgaggtgctt caatgcccc	840
tttccatgcg tgccttgtga tgggtgtgct tcaattaata tagatcgttt tgcttttcaa	900
aacttgacct aacttcgata cctaaacctc tctagcactt cctcaggaa gattaatgct	960
gcctgggtta aaaatatgcc tcatctgaag gtgctggatc ttgaattcaa ctatttagtg	1020
ggagaaatag cctctggggc atttttaacg atgctgcccc gcttagaaat acttgacttg	1080
tcttttaact atataaaggg gagttatcca cagcatatta atatttccag aaacttctct	1140
aaacttttgt ctctacgggc attgcattta agaggttatg tgttccagga actcagagaa	1200
gatgatttcc agccctgat gcagctcca aacttatcga ctatcaactt gggattaat	1260
tttattaagc aaatcgattt caaacttttc caaaatttct ccaatctgga aattatttac	1320
ttgtcagaaa acagaatata accgttggtg aaagataccc ggcagagtta tgcaaatagt	1380
tcctcttttc aacgtcatat ccggaaacga cgctcaacag attttgagtt tgaccacat	1440
tcgaactttt atcatttcac ccgtccttta ataaagccac aatgtgctgc ttatggaaaa	1500
gccttagatt taagcctcaa cagtatttct ttcattgggc caaaccaatt tgaaaatctt	1560
cctgacattg cctgtttaaa tctgtctgca aatagcaatg ctcaagtgtt aagtggaaact	1620
gaattttcag ccattcctca tgtcaaatat ttggatttga caaacaatag actagacttt	1680
gataatgcta gtgctcttac tgaattgtcc gacttggaag ttctagatct cagctataat	1740
tcacactatt tcagaatagc aggcgtaaca catcatctag aatttattca aaatttcaca	1800
aatctaaaag ttttaaaact gagccacaac aacatttata ctttaacaga taagtataac	1860
ctggaaagca agtccctggt agaattagtt ttcagtggca atcgccctga cattttgtgg	1920
aatgatgatg acaacaggta tatctccatt ttcaaaggtc tcaagaatct gacacgtctg	1980
gatttatccc ttaataggct gaagcacatc ccaaataag cattccttaa tttgccagcg	2040
agtctcactg aactacatat aaatgataat atgttaaagt tttttaactg gacattactc	2100
cagcagttcc ctcgctcga gttgcttgac ttacgtggaa acaaactact ctttttaact	2160
gatagcctat ctgactttac atcttccctt cggacactgc tgctgagtca taacaggatt	2220
tcccacctac cctctggctt tctttctgaa gtcagtagtc tgaagcacct cgatttaagt	2280
tccaatctgc taaaaacaat caacaaatcc gcacttgaaa ctaagaccac caccaaatta	2340
tctatgttgg aactacacgg aaaccctttt gaatgcacct gtgacattgg agatttccga	2400
agatggatgg atgaacatct gaatgtcaaa attcccagac tggtagatgt catttgtgcc	2460

agtcctgggg atcaaagagg gaagagtatt gtgagtctgg agctgacaac ttgtgtttca 2520
 gatgtcactg cagtgatatt atttttcttc acgttcttta tcaccaccat ggttatgttg 2580
 gctgccctgg ctcaccattt gttttactgg gatgtttggg ttatatataa tgtgtgttta 2640
 gctaaggtaa aaggctacag gtctctttcc acatcccaaa ctttctatga tgcttacatt 2700
 tcttatgaca ccaaagatgc ctctgttact gactgggtga taaatgagct gcgctaccac 2760
 cttgaagaga gccgagacaa aaacgttctc ctttgtctag aggagagggg ttgggacccg 2820
 ggattggcca tcacgacaa cctcatgcag agcatcaacc aaagcaagaa aacagtattt 2880
 gttttaacca aaaaatatgc aaaaagctgg aactttaaaa cagcttttta cttggctttg 2940
 cagaggctaa tggatgagaa catggatgtg attatattta tcctgctgga gccagtgtta 3000
 cagcattctc agtatttgag gctacggcag cggatctgta agagctccat cctccagtgg 3060
 cctgacaacc cgaaggcaga aggcttgttt tggcaaactc tgagaaatgt ggtcttgact 3120
 gaaaatgatt cacggtataa caatatgtat gtcgattcca ttaagcaata ctaactgacg 3180
 ttaagtcatg atttcgcgcc ataataaaga tgcaaaggaa tgacatttct gtattagtta 3240
 tctattgcta tgtaacaaat tatcccaaaa cttagtgggt taaaacaaca catttgctgg 3300
 cccacagttt t 3311

<210> 47
 <211> 3367
 <212> DNA
 <213> Homo sapiens

<400> 47
 ctccctgcata gagggtagca ttctgcgctg ctgcaagtta cggaatgaaa aattagaaca 60
 acagaaacgt gggtctcttg acacttcagt gttagggaac atcagcaaga cccatcccag 120
 gagaccttga aggaagcctt tgaaaggag aatgaaggag tcactcttgc aaaatagctc 180
 ctgcagcctg ggaaaggaga ctaaaaagga aaacatgttc cttcagtcgt caatgctgac 240
 ctgcattttc ctgctaatat ctgggttcctg tgagttatgc gccgaagaaa atttttctag 300
 aagctatcct tgtgatgaga aaaagcaaaa tgactcagtt attgcagagt gcagcaatcg 360
 tcgactacag gaagttcccc aaacgggtggg caaatatgtg acagaactag acctgtctga 420
 taatttcatc acacacataa cgaatgaatc atttcaaggg ctgcaaaatc tcactaaaat 480
 aatctaaac cacaaccca atgtacagca ccagaacgga aatcccggta tacaatcaaa 540
 tggcttgaat atcacagacg gggcattcct caacctaaaa aacctaaggg agttactgct 600
 tgaagacaac cagttacccc aaataccctc tggtttgcca gagtctttga cagaacttag 660
 tctaattcaa aacaatatat acaacataac taaagagggc atttcaagac ttataaactt 720

gaaaaatctc	tatttggcct	ggaactgcta	ttttaacaaa	gtttgcgaga	aaactaacat	780	
agaagatgga	gtatttgaaa	cgctgacaaa	tttgagattg	ctatcactat	ctttcaattc	840	
tctttcacac	gtgtcaccca	aactgccaag	ctccctacgc	aaactttttc	tgagcaacac	900	
ccagatcaaa	tacattagtg	aagaagatth	caagggattg	ataaatttaa	cattactaga	960	
tttaagcggg	aactgtccga	gggtgcttca	tgccccattt	ccatgcgtgc	cttgtgatgg	1020	
tggtgcttca	attaatatag	atcgttttgc	ttttcaaaac	ttgacccaac	ttcgatacct	1080	
aaacctctct	agcacttccc	tcaggaagat	taatgctgcc	tggtttaaaa	atatgcctca	1140	
tctgaagggtg	ctggatcttg	aattcaacta	tttagtgggg	gaaatagcct	ctggggcatt	1200	
tttaacgatg	ctgccccgct	tagaaatact	tgacttgtct	tttaactata	taaaggggag	1260	
ttatccacag	catattaata	tttccagaaa	cttctctaaa	cctttgtctc	tacgggcatt	1320	
gcatttaaga	ggttatgtgt	tccaggaact	cagagaagat	gatttccagc	ccctgatgca	1380	
gcttccaaac	ttatcgacta	tcaacttggg	tattaatttt	attaagcaaa	tcgatttcaa	1440	
actttttcaa	aattttctca	atctggaaat	tatttacttg	tcagaaaaca	gaatatcacc	1500	
gttggtaaaa	gatacccggc	agagttatgc	aaatagttcc	tcttttcaac	gtcatatccg	1560	
gaaacgacgc	tcaacagatt	ttgagtttga	cccacattcg	aacttttatc	atttcacccg	1620	
tcctttaata	aagccacaat	gtgctgctta	tggaagagcc	ttagatttaa	gcctcaacag	1680	
tattttcttc	attggggcaa	accaatttga	aaatcttcc	gacattgcct	gtttaaatct	1740	
gtctgcaa	at	agcaatgctc	aagtgttaag	tggaactgaa	ttttcagcca	ttcctcatgt	1800
caaataatttg	gatttgacaa	acaatagact	agactttgat	aatgctagt	ctcttactga	1860	
attgtccgac	ttggaagtcc	tagatctcag	ctataattca	cactatttca	gaatagcagg	1920	
cgtaacacat	catctagaat	ttattcaaaa	tttcacaaat	ctaaaagttt	taaacttgag	1980	
ccacaacaac	atttatactt	taacagataa	gtataacctg	gaaagcaagt	ccctggtaga	2040	
attagttttc	agtggcaatc	gccttgacat	tttgtggaat	gatgatgaca	acaggatat	2100	
ctccattttc	aaaggtctca	agaatctgac	acgtctggat	ttatccctta	ataggctgaa	2160	
gcacatccca	aatgaagcat	tccttaattt	gccagcgagt	ctcactgaac	tacatatata	2220	
tgataatatg	ttaaagtttt	tttaactggac	attactccag	cagtttctc	gtctcgagtt	2280	
gcttgactta	cgtggaaaca	aactactctt	tttaactgat	agcctatctg	actttacatc	2340	
ttcccttcgg	acactgctgc	tgagtcataa	caggatttcc	cacctacct	ctggctttct	2400	
ttctgaagtc	agtagtctga	agcacctcga	tttaagttcc	aatctgctaa	aaacaatcaa	2460	
caaatccgca	cttgaaacta	agaccaccac	caaattatct	atgttggaac	tacacggaaa	2520	
cccctttgaa	tgcacctgtg	acattggaga	tttccgaaga	tggttggtg	aacatctgaa	2580	
tgtcaaaatt	cccagactgg	tagatgtcat	ttgtgccagt	cctggggatc	aaagagggaa	2640	

```

gagtattgtg agtctggagc taacaacttg tgtttcagat gtcactgcag tgatattatt 2700
tttcttcacg ttctttatca ccaccatggg tatgttggtt gccctggctc accatttggt 2760
ttactgggat gtttggttta tatataatgt gtgttttagct aagataaaag gctacaggctc 2820
tctttccaca tcccaaactt tctatgatgc ttacatttct tatgacacca aagatgcctc 2880
tgttactgac tgggtgataa atgagctgcg ctaccacctt gaagagagcc gagacaaaaa 2940
cgttctcctt tgtctagagg agagggattg ggaccggga ttggccatca tcgacaacct 3000
catgcagagc atcaacccaa gcaagaaaac agtatttggt ttaacccaaa aatatgcaaa 3060
aagctggaac tttaaaacag ctttttactt ggctttgcag aggctaattg atgagaacat 3120
ggatgtgatt atatttatcc tgctggagcc agtgttacag cattctcagt atttgaggct 3180
acggcagcgg atctgtaaga gctccatcct ccagtggcct gacaaccga aggagaagg 3240
cttgtttttg caaactctga gaaatgtggt cttgactgaa aatgattcac ggtataacaa 3300
tatgtatgtc gattccatta agcaatacta actgacgtta agtcatgatt tcgcgccata 3360
ataaaga 3367

```

<210> 48

<211> 4211

<212> DNA

<213> Homo sapiens

<400> 48

```

ctcctgcata gaggtacca ttctgcgtg ctgcaagtta cggaatgaaa aattagaaca 60
acagaaacat ggaaacatg ttcttcagt cgtcaatgct gacctgcatt ttctgctaa 120
tatctggttc ctgtgagtta tgcgccgaag aaaattttct tagaagctat ccttgtgatg 180
agaaaaagca aaatgactca gttattgcag agtgcagcaa tcgtcgacta caggaagttc 240
cccaaacggg gggcaaatat gtgacagaac tagacctgtc tgataatttc atcacacaca 300
taacgaatga atcatttcaa gggctgcaaa atctcactaa aataaatcta aaccacaacc 360
ccaatgtaca gcaccagaac ggaaatcccg gtatacaatc aaatggcttg aatatcacag 420
acggggcatt cctcaacctt aaaaacctaa gggagtact gcttgaagac aaccagttac 480
cccaaatacc ctctggtttg ccagagtctt tgacagaact tagtctaatt caaaacaata 540
tatacaacat aactaaagag ggcatttcaa gacttataaa cttgaaaaat ctctatttg 600
cctggaactg ctattttaac aaagtgtgcg agaaaactaa catagaagat ggagtatttg 660
aaacgctgac aaatttgag ttgctatcac tatctttcaa ttctctttca cacgtgccac 720
ccaaactgcc aagctcccta cgaaaacttt ttctgagcaa caccagatc aaatacatta 780
gtgaagaaga tttcaaggga ttgataaatt taacattact agatttaagc gggaactgtc 840

```


cgaggtgctt caatgcccc tttccatgcg tgccttgtga tgggtggtgct tcaattaata	900
tagatcgttt tgcttttcaa aacttgaccc aacttcgata cctaaacctc tctagcactt	960
ccctcaggaa gattaatgct gcctgggttta aaaatatgcc tcatctgaag gtgctggatc	1020
ttgaattcaa ctatttagtg ggagaaatag cctctggggc atttttaacg atgctgcccc	1080
gcttagaaat acttgacttg tcttttaact atataaaggg gagttatcca cagcatatta	1140
atatttccag aaacttctct aaacttttgt ctctacgggc attgcattta agaggttatg	1200
tgttccagga actcagagaa gatgatttcc agccctgat gcagcttcca aacttatcga	1260
ctatcaactt ggggtattaat ttattaagc aaatcgattt caaacttttc caaaatttct	1320
ccaatctgga aattatttac ttgtcagaaa acagaatatc accgttggtta aaagatacc	1380
ggcagagtta tgcaaatagt tcctcttttc aacgtcatat ccggaacga cgctcaacag	1440
attttgagtt tgaccacat tcgaactttt atcatttcac ccgtccttta ataaagccac	1500
aatgtgctgc ttatggaaaa gccttagatt taagcctcaa cagtattttc ttcattgggc	1560
caaaccaatt tgaaaatctt cctgacattg cctgtttaaa tctgtctgca aatagcaatg	1620
ctcaagtgtt aagtggaact gaattttcag ccattcctca tgtcaaataat ttggatttga	1680
caaacaatag actagacttt gataatgcta gtgctcttac tgaattgtcc gacttggaag	1740
ttctagatct cagctataat tcacactatt tcagaatagc aggcgtaaca catcatctag	1800
aatttattca aaatttcaca aatctaaaag ttttaaactt gagccacaac aacatttata	1860
ctttaacaga taagtataac ctggaaagca agtccctggg agaattagtt ttcagtggca	1920
atgccttga cattttgtgg aatgatgatg acaacaggta tatctccatt ttcaaaggct	1980
tcaagaatct gacacgtctg gatttatccc ttaataggct gaagcacatc ccaaatgaag	2040
cattccttaa tttgccagcg agtctcactg aactacatat aaatgataat atgttaaagt	2100
tttttaactg gacattactc cagcagtttc ctctctcga gttgcttgac ttacgtggaa	2160
acaaactact ctttttaact gatagcctat ctgactttac atcttccctt cggacactgc	2220
tgctgagtca taacaggatt tcccacctac cctctggctt tctttctgaa gtcagtagtc	2280
tgaagcacct cgatttaagt tccaatctgc taaaaacaat caacaaatcc gcacttgaaa	2340
ctaagaccac caccaaatta tctatgttgg aactacacgg aaaccctttt gaatgcacct	2400
gtgacattgg agatttccga agatggatgg atgaacatct gaatgtcaaa attcccagac	2460
tggtagatgt catttgtgcc agtcctgggg atcaaagagg gaagagtatt gtgagtctgg	2520
agetaacaac ttgtgtttca gatgtcactg cagtgatatt atttttcttc acgttcttta	2580
tcaccaccat ggttatgttg gctgccttgg ctccacattt gttttactgg gatgtttgg	2640
ttatatataa tgttgtttta gctaaggtaa aaggctacag gtctctttcc acatcccaaa	2700
ctttctatga tgcttacatt tcttatgaca ccaaagatgc ctctgttact gactgggtga	2760

```

taaatgagct gcgctaccac cttgaagaga gccgagacaa aaacgttctc ctttgtctag 2820
aggagagggga ttgggatccg ggattggcca tcatcgacaa cctcatgcag agcatcaacc 2880
aaagcaagaa aacagtatth gttttaacca aaaaatatgc aaaaagctgg aactttaaaa 2940
cagcttttta cttggctttg cagaggctaa tggatgagaa catggatgtg attatatthta 3000
tcctgctgga gccagtgtta cagcattctc agtatttgag gctacggcag cggatctgta 3060
agagctccat cctccagtgg cctgacaacc cgaaggcaga aggettgtht tggcaaactc 3120
tgagaaatgt ggtcttgact gaaaatgatt cacggtataa caatatgtat gtcgattcca 3180
ttaagcaata ctaactgacg ttaagtcatg atttcgcgcc ataataaaga tgcaaaggaa 3240
tgacatttht gtattagtta tctattgcta tgtaacaaat tatcccaaaa cttagtggth 3300
taaaacaaca catttgctgg ccacagtht ttgagggthc ggagtccagg ccacagcataa 3360
ctgggtctc tgctcagggt gtctcagagg ctgcaatgta ggtgttcacc agagacatag 3420
gcatcactgg ggtcacactc atgtggtgt tttctggatt caattcctcc tgggctattg 3480
gccaaaggct atactcatgt aagccatgcg agcctctccc acaaggcagc ttgcttcac 3540
agagctagca aaaaagagag gttgctagca agatgaagtc acaatcttht gtaatcgaat 3600
caaaaaagtg atatctcatc actttggcca tattctatth gttagaagta aaccacaggt 3660
cccaccagct ccatgggagt gaccacctca gtccaggga aacagctgaa gaccaagatg 3720
gtgagctctg attgcttcag ttggtcatca actatthtcc cttgactgct gtctgggat 3780
ggctgctat cttgatgata gattgtgaat atcaggaggc agggatcact gtggaccatc 3840
ttagcagthg acctaacaca tcttcttht aatatctaag aactthtgcc actgtgacta 3900
atggtcctaa tattaagctg ttgtttatat ttatcatata tctatggcta catggttata 3960
ttatgctgtg gttgcgttcg gttttatthta cagttgctth taaaaatatt tgctgtaaca 4020
tttgacttht aaggthttaga tgccattthaa gaactgagat ggatagctth taaagcatct 4080
tttacttht accatthttht aaaagtatgc agctaaattc gaagctthtg gtctatattg 4140
ttaattgcca ttgctgtaaa tcttaaatg aatgaataaa aatgtthcat tttacaaaaa 4200
aaaaaaaaa a 4211

```

```

<210> 49
<211> 3468
<212> DNA
<213> Homo sapiens

```

```

<400> 49
ctcctgcata gagggtagca ttctgcgtg ctgcaagtta cggaatgaaa aattagaaca 60
acagaaacat ggttctcttg acacttcagt gttagggaac atcagcaaga cccatcccag 120

```

```

gagaccttga aggaagcctt tgaaagggag aatgaaggag tcacctttgc aaaatagctc 180
ctgcagcctg ggaaaggaga ctaaaaagga aaacatgttc cttcagtcgt caatgctgac 240

ctgcattttc ctgctaatat ctggttcctg tgagttatgc gccgaagaaa atttttctag 300
aagctatcct tgtgatgaga aaaagcaaaa tgactcagtt attgcagagt gcagcaatcg 360
tcgactacag gaagttcccc aaacggtggg caaatatgtg acagaactag acctgtctga 420
taatttcac acacacataa cgaatgaatc atttcaaggg ctgcaaaatc tcactaaaat 480
aatctaaac cacaaccca atgtacagca ccagaacgga aatcccggta tacaatcaaa 540
tggcttgaat atcacagacg gggcattcct caacctaaaa aacctagggt agttactgct 600
tgaagacaac cagttacccc aaataccctc tggtttgcca gagtctttga cagaacttag 660
tctaattcaa aacaatatat acaacataac taaagagggc atttcaagac ttataaactt 720
gaaaaatctc tatttggcct ggaactgcta ttttaacaaa gtttgcgaga aaactaacat 780
agaagatgga gtatttgaaa cgctgacaaa tttggagttg ctatcactat ctttcaattc 840
tctttcacac gtgccacca aactgccaa gctccctacgc aaactttttc tgagcaaac 900
ccagatcaaa tacattagtg aagaagattt caagggttg ataaatttaa cattactaga 960
tttaagcggg aactgtccga ggtgcttcaa tgccccattt ccatgcgtgc cttgtgatgg 1020
tgggtgcttca attaatatag atcgttttgc ttttcaaaac ttgaccaaac ttcgatacct 1080
aaacctctct agcacttccc tcaggaagat taatgctgcc tggtttaaaa atatgcctca 1140
tctgaagggt ctggatcttg aattcaacta tttagtggga gaaatagcct ctggggcatt 1200
tttaacgatg ctgccccgct tagaaatact tgacttgtct tttaactata taaaggggag 1260
ttatccacag catattaata tttccagaaa cttctctaaa cttttgtctc tacgggcatt 1320
gcatttaaga ggttatgtgt tccaggaact cagagaagat gatttccagc ccctgatgca 1380
gcttccaaac ttatcgacta tcaacttggg tattaatttt attaagcaaa tcgatttcaa 1440
acttttccaa aattttctca atctggaaat tatttacttg tcagaaaaca gaatatcacc 1500
gttggttaaaa gataccgggc agagtatatg aaatagttcc tcttttcaac gtcatatccg 1560
gaaacgacgc tcaacagatt ttgagtttga cccacattcg aacttttatc atttcacccg 1620
tcctttaata aagccacaat gtgctgctta tggaaaagcc ttagatttaa gcctcaacag 1680
tattttcttc attgggccaa accaatttga aaatcttccg gacattgcct gtttaaactc 1740
gtctgcaaat agcaatgctc aagtgttaag tggaactgaa ttttcagcca ttcctcatgt 1800
caaataattg gatttgacaa acaatagact agactttgat aatgctagtg ctcttactga 1860
attgtccgac ttggaagtgc tagatctcag ctataattca cactatttca gaatagcagg 1920
cgtaacacat catctagaat ttattcaaaa tttcacaat ctaaaagtgt taaacttgag 1980
ccacaacaac atttatactt taacagataa gtataacctg gaaagcaagt ccctggtaga 2040

```

```

attagttttc agtggcaatc gccttgacat tttgtggaat gatgatgaca acaggtatat 2100
ctccattttc aaaggtctca agaactctgac acgtctggat ttatccctta ataggctgaa 2160
gcacatccca aatgaagcat tccttaattt gccagcgagt ctactgaac tacatataaa 2220
tgataatatg ttaaagtttt ttaactggac attactccag cagtttcctc gtctcgagtt 2280
gcttgactta cgtggaaaca aactactctt tttaactgat agcctatctg actttacatc 2340
ttcccttcgg acactgctgc tgagtcataa caggatttcc cacctaccct ctggctttct 2400
ttctgaagtc agtagtctga agcacctcga tttaagttcc aatctgctaa aaacaatcaa 2460
caaatccgca cttgaaacta agaccaccac caaattatct atgttggaac tacacggaaa 2520
cccctttgaa tgcacctgtg acattggaga ttccgaaga tggatggatg aacatctgaa 2580
tgtcaaaatt ccagactgg tagatgtcat ttgtgccagt cctggggatc aaagagggaa 2640
gagtattgtg agtctggagc taacaacttg tgtttcagat gtcactgcag tgatattatt 2700
ttcttccagc ttctttatca ccaccatggt tatgttggtt gccctggctc accatttggt 2760
ttactgggat gtttggttta tatataatgt gtgttttagct aaggtaaaag gctacaggtc 2820
tctttccaca tcccaaactt tctatgatgc ttacatttct tatgacacca aagatgcctc 2880
tgttactgac tgggtgataa atgagctgcg ctaccacctt gaagagagcc gagacaaaaa 2940
cgttctcctt tgtctagagg agagggattg ggatccggga ttggccatca tcgacaacct 3000
catgcagagc atcaacccaa gcaagaaaac agtatttggt ttaacccaaa aatatgcaaa 3060
aagctggaac tttaaaacag ctttttactt ggctttgcag aggctaattg atgagaacat 3120
ggatgtgatt atatttatcc tgctggagcc agtgttacag cattctcagt atttgaggt 3180
acggcagcgg atctgtaaga gctccatcct ccagtggcct gacaaccgga aggcagaagg 3240
cttgttttgg caaactctga gaaatgtggt cttgactgaa aatgattcac ggtataacaa 3300
tatgtatgtc gattccatta agcaatacta actgacgtta agtcatgatt tcgcgccata 3360
ataaagatgc aaaggaatga catttctgta ttagttatct attgctatgt aacaaattat 3420
cccaaaactt agtgggttaa aacaacacat ttgctggccc acagtttt 3468

```

<210> 50

<211> 1041

<212> PRT

<213> Homo sapiens

<400> 50

```

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
1           5           10          15

```

```

Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
          20          25          30

```

Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
 35 40 45
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
 50 55 60
 Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
 65 70 75 80
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
 85 90 95
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
 100 105 110
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
 115 120 125
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
 130 135 140
 Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
 145 150 155 160
 Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
 165 170 175
 Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
 180 185 190
 Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
 195 200 205
 Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
 210 215 220
 Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
 225 230 235 240
 Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
 245 250 255
 Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
 260 265 270
 Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
 275 280 285
 Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
 290 295 300
 Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
 305 310 315 320
 Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
 325 330 335
 Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
 340 345 350
 Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser

355 360 365
 Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
 370 375 380
 Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
 385 390 395 400
 Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
 405 410 415
 Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
 420 425 430
 Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
 435 440 445
 Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
 450 455 460
 Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
 465 470 475 480
 Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
 485 490 495
 Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
 500 505 510
 Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala
 515 520 525
 Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
 530 535 540
 Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
 545 550 555 560
 Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
 565 570 575
 Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
 580 585 590
 His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
 595 600 605
 Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
 610 615 620
 Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
 625 630 635 640
 Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
 645 650 655
 Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
 660 665 670
 Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
 675 680 685
 Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr

Asp 705	Ser 705	Leu 705	Ser 705	Asp 705	Phe 710	Thr 710	Ser 710	Ser 710	Leu 710	Arg 715	Thr 715	Leu 715	Leu 715	Leu 715	Ser 720
His 725	Asn 725	Arg 725	Ile 725	Ser 725	His 725	Leu 725	Pro 725	Ser 725	Gly 730	Phe 730	Leu 730	Ser 730	Glu 735	Val 735	Ser 735
Ser 740	Leu 740	Lys 740	His 740	Leu 740	Asp 740	Leu 740	Ser 740	Ser 745	Asn 745	Leu 745	Leu 745	Lys 745	Thr 750	Ile 750	Asn 750
Lys 755	Ser 755	Ala 755	Leu 755	Glu 755	Thr 755	Lys 755	Thr 760	Thr 760	Thr 760	Lys 760	Leu 760	Ser 765	Met 765	Leu 765	Glu 765
Leu 770	His 770	Gly 770	Asn 770	Pro 770	Phe 770	Glu 775	Cys 775	Thr 775	Cys 775	Asp 775	Ile 780	Gly 780	Asp 780	Phe 780	Arg 780
Arg 785	Trp 785	Met 785	Asp 785	Glu 785	His 790	Leu 790	Asn 790	Val 790	Lys 790	Ile 795	Pro 795	Arg 795	Leu 795	Val 795	Asp 800
Val 805	Ile 805	Cys 805	Ala 805	Ser 805	Pro 805	Gly 805	Asp 805	Gln 810	Arg 810	Gly 810	Lys 810	Ser 810	Ile 815	Val 815	Ser 815
Leu 820	Glu 820	Leu 820	Thr 820	Thr 820	Cys 820	Val 820	Ser 820	Asp 825	Val 825	Thr 825	Ala 825	Val 825	Ile 830	Leu 830	Phe 830
Phe 835	Phe 835	Thr 835	Phe 835	Phe 835	Ile 835	Thr 840	Thr 840	Met 840	Val 840	Met 840	Leu 840	Ala 845	Ala 845	Leu 845	Ala 845
His 850	His 850	Leu 850	Phe 850	Tyr 850	Trp 850	Asp 855	Val 855	Trp 855	Phe 855	Ile 860	Tyr 860	Asn 860	Val 860	Cys 860	Leu 860
Ala 865	Lys 865	Val 865	Lys 865	Gly 865	Tyr 870	Arg 870	Ser 870	Leu 870	Ser 870	Thr 875	Ser 875	Gln 875	Thr 875	Phe 880	Tyr 880
Asp 885	Ala 885	Tyr 885	Ile 885	Ser 885	Tyr 885	Asp 885	Thr 885	Lys 885	Asp 890	Ala 890	Ser 890	Val 890	Thr 890	Asp 895	Trp 895
Val 900	Ile 900	Asn 900	Glu 900	Leu 900	Arg 900	Tyr 900	His 900	Leu 905	Glu 905	Glu 905	Ser 905	Arg 905	Asp 910	Lys 910	Asn 910
Val 915	Leu 915	Leu 915	Cys 915	Leu 915	Glu 915	Glu 915	Arg 915	Asp 920	Trp 920	Asp 920	Pro 920	Gly 925	Leu 925	Ala 925	Ile 925
Ile 930	Asp 930	Asn 930	Leu 930	Met 930	Gln 930	Ser 935	Ile 935	Asn 935	Gln 935	Ser 935	Lys 940	Lys 940	Thr 940	Val 940	Phe 940
Val 945	Leu 945	Thr 945	Lys 945	Lys 945	Tyr 950	Ala 950	Lys 950	Ser 950	Trp 950	Asn 955	Phe 955	Lys 955	Thr 955	Ala 960	Phe 960
Tyr 965	Leu 965	Ala 965	Leu 965	Gln 965	Arg 965	Leu 965	Met 965	Asp 965	Glu 970	Asn 970	Met 970	Asp 970	Val 970	Ile 975	Ile 975
Phe 980	Ile 980	Leu 980	Leu 980	Glu 980	Pro 980	Val 980	Leu 980	Gln 985	His 985	Ser 985	Gln 985	Tyr 985	Leu 990	Arg 990	Leu 990
Arg 995	Gln 995	Arg 995	Ile 995	Cys 995	Lys 995	Ser 995	Ser 995	Ile 1000	Leu 1000	Gln 1000	Trp 1000	Pro 1005	Asp 1005	Asn 1005	Pro 1005
Lys 1010	Ala 1010	Glu 1010	Gly 1010	Leu 1010	Phe 1010	Trp 1015	Gln 1015	Thr 1015	Leu 1015	Arg 1015	Asn 1020	Val 1020	Val 1020	Leu 1020	
Thr 1025	Glu 1025	Asn 1025	Asp 1025	Ser 1025	Arg 1025	Tyr 1025	Asn 1025	Asn 1025	Met 1025	Tyr 1025	Val 1025	Asp 1025	Ser 1025	Ile 1025	

1025
Lys Gln Tyr
1040

1030

1035

<210> 51
<211> 1059
<212> PRT
<213> Homo sapiens

<400> 51

Met Lys Glu Ser Ser Leu Gln Asn Ser Ser Cys Ser Leu Gly Lys Glu
1 5 10 15
Thr Lys Lys Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile
20 25 30
Phe Leu Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe
35 40 45
Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile
50 55 60
Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly
65 70 75 80
Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile
85 90 95
Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu
100 105 110
Asn His Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln
115 120 125
Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn
130 135 140
Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser
145 150 155 160
Gly Leu Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile
165 170 175
Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn
180 185 190
Leu Tyr Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr
195 200 205
Asn Ile Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu
210 215 220
Ser Leu Ser Phe Asn Ser Leu Ser His Val Ser Pro Lys Leu Pro Ser
225 230 235 240
Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser
245 250 255
Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser
260 265 270

Gly Asn Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys
 275 280 285
 Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu
 290 295 300
 Thr Gln Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile
 305 310 315 320
 Asn Ala Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu
 325 330 335
 Glu Phe Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr
 340 345 350
 Met Leu Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys
 355 360 365
 Gly Ser Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Pro
 370 375 380
 Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu
 385 390 395 400
 Arg Glu Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr
 405 410 415
 Ile Asn Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe
 420 425 430
 Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile
 435 440 445
 Ser Pro Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser
 450 455 460
 Phe Gln Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp
 465 470 475 480
 Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln
 485 490 495
 Cys Ala Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe
 500 505 510
 Phe Ile Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu
 515 520 525
 Asn Leu Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe
 530 535 540
 Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu
 545 550 555 560
 Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val
 565 570 575
 Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr
 580 585 590
 His His Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn

595 600 605
 Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu
 610 615 620
 Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile
 625 630 635 640
 Leu Trp Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu
 645 650 655
 Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile
 660 665 670
 Pro Asn Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His
 675 680 685
 Ile Asn Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln
 690 695 700
 Phe Pro Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe
 705 710 715 720
 Leu Thr Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu
 725 730 735
 Leu Ser His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu
 740 745 750
 Val Ser Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr
 755 760 765
 Ile Asn Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met
 770 775 780
 Leu Glu Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp
 785 790 795 800
 Phe Arg Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu
 805 810 815
 Val Asp Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile
 820 825 830
 Val Ser Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile
 835 840 845
 Leu Phe Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala
 850 855 860
 Leu Ala His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val
 865 870 875 880
 Cys Leu Ala Lys Ile Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr
 885 890 895
 Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr
 900 905 910
 Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp
 915 920 925
 Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu

930 935 940
 Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr
 945 950 955 960
 Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr
 965 970 975
 Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val
 980 985 990
 Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu
 995 1000 1005
 Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro
 1010 1015 1020
 Asp Asn Pro Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn
 1025 1030 1035
 Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val
 1040 1045 1050
 Asp Ser Ile Lys Gln Tyr
 1055

<210> 52
 <211> 1041
 <212> PRT
 <213> Homo sapiens

<400> 52

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
 1 5 10 15
 Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
 20 25 30
 Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
 35 40 45
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
 50 55 60
 Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
 65 70 75 80
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
 85 90 95
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
 100 105 110
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
 115 120 125
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
 130 135 140
 Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
 145 150 155 160

Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
165 170 175

Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
180 185 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
195 200 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
210 215 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225 230 235 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
245 250 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
260 265 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
275 280 285

Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
290 295 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305 310 315 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
325 330 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
340 345 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
355 360 365

Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
370 375 380

Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
385 390 395 400

Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
405 410 415

Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
420 425 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
435 440 445

Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
450 455 460

Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
465 470 475 480

Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile

Gly	Pro	Asn	Gln	Phe	Glu	Asn	Leu	Pro	Asp	Ile	Ala	Cys	Leu	Asn	Leu	485 500	490 505	495 510
Ser	Ala	Asn	Ser	Asn	Ala	Gln	Val	Leu	Ser	Gly	Thr	Glu	Phe	Ser	Ala	515	520	525
Ile	Pro	His	Val	Lys	Tyr	Leu	Asp	Leu	Thr	Asn	Asn	Arg	Leu	Asp	Phe	530		540
Asp	Asn	Ala	Ser	Ala	Leu	Thr	Glu	Leu	Ser	Asp	Leu	Glu	Val	Leu	Asp	545	550	555
Leu	Ser	Tyr	Asn	Ser	His	Tyr	Phe	Arg	Ile	Ala	Gly	Val	Thr	His	His		565	570
Leu	Glu	Phe	Ile	Gln	Asn	Phe	Thr	Asn	Leu	Lys	Val	Leu	Asn	Leu	Ser		580	585
His	Asn	Asn	Ile	Tyr	Thr	Leu	Thr	Asp	Lys	Tyr	Asn	Leu	Glu	Ser	Lys	595	600	605
Ser	Leu	Val	Glu	Leu	Val	Phe	Ser	Gly	Asn	Arg	Leu	Asp	Ile	Leu	Trp	610	615	620
Asn	Asp	Asp	Asp	Asn	Arg	Tyr	Ile	Ser	Ile	Phe	Lys	Gly	Leu	Lys	Asn	625	630	635
Leu	Thr	Arg	Leu	Asp	Leu	Ser	Leu	Asn	Arg	Leu	Lys	His	Ile	Pro	Asn		645	650
Glu	Ala	Phe	Leu	Asn	Leu	Pro	Ala	Ser	Leu	Thr	Glu	Leu	His	Ile	Asn		660	665
Asp	Asn	Met	Leu	Lys	Phe	Phe	Asn	Trp	Thr	Leu	Leu	Gln	Gln	Phe	Pro	675	680	685
Arg	Leu	Glu	Leu	Leu	Asp	Leu	Arg	Gly	Asn	Lys	Leu	Leu	Phe	Leu	Thr	690	695	700
Asp	Ser	Leu	Ser	Asp	Phe	Thr	Ser	Ser	Leu	Arg	Thr	Leu	Leu	Leu	Ser	705	710	715
His	Asn	Arg	Ile	Ser	His	Leu	Pro	Ser	Gly	Phe	Leu	Ser	Glu	Val	Ser		725	730
Ser	Leu	Lys	His	Leu	Asp	Leu	Ser	Ser	Asn	Leu	Leu	Lys	Thr	Ile	Asn		740	745
Lys	Ser	Ala	Leu	Glu	Thr	Lys	Thr	Thr	Thr	Lys	Leu	Ser	Met	Leu	Glu	755	760	765
Leu	His	Gly	Asn	Pro	Phe	Glu	Cys	Thr	Cys	Asp	Ile	Gly	Asp	Phe	Arg	770	775	780
Arg	Trp	Met	Asp	Glu	His	Leu	Asn	Val	Lys	Ile	Pro	Arg	Leu	Val	Asp	785	790	795
Val	Ile	Cys	Ala	Ser	Pro	Gly	Asp	Gln	Arg	Gly	Lys	Ser	Ile	Val	Ser		805	810
Leu	Glu	Leu	Thr	Thr	Cys	Val	Ser	Asp	Val	Thr	Ala	Val	Ile	Leu	Phe			

820 825 830
 Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
 835 840 845
 His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
 850 855 860
 Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
 865 870 875 880
 Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
 885 890 895
 Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
 900 905 910
 Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
 915 920 925
 Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
 930 935 940
 Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
 945 950 955 960
 Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
 965 970 975
 Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
 980 985 990
 Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
 995 1000 1005
 Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
 1010 1015 1020
 Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile
 1025 1030 1035
 Lys Gln Tyr
 1040

<210> 53
 <211> 1041
 <212> PRT
 <213> Homo sapiens

<400> 53

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
 1 5 10 15
 Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
 20 25 30
 Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
 35 40 45
 Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
 50 55 60

Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
 65 70 75 80
 Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
 85 90 95
 Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
 100 105 110
 Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
 115 120 125
 Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
 130 135 140
 Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
 145 150 155 160
 Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
 165 170 175
 Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
 180 185 190
 Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
 195 200 205
 Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
 210 215 220
 Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
 225 230 235 240
 Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
 245 250 255
 Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
 260 265 270
 Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
 275 280 285
 Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
 290 295 300
 Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
 305 310 315 320
 Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
 325 330 335
 Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
 340 345 350
 Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
 355 360 365
 Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
 370 375 380
 Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn

385 390 395 400
 Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
 405 410 415
 Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
 420 425 430
 Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
 435 440 445
 Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
 450 455 460
 Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
 465 470 475 480
 Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
 485 490 495
 Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
 500 505 510
 Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala
 515 520 525
 Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
 530 535 540
 Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
 545 550 555 560
 Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
 565 570 575
 Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
 580 585 590
 His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
 595 600 605
 Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
 610 615 620
 Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
 625 630 635 640
 Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
 645 650 655
 Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
 660 665 670
 Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
 675 680 685
 Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr
 690 695 700
 Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
 705 710 715 720
 His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
 725 730 735
 740 745 750
 Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
 755 760 765
 Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
 770 775 780
 Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
 785 790 795 800
 Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
 805 810 815
 Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe
 820 825 830
 Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
 835 840 845
 His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
 850 855 860
 Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
 865 870 875 880
 Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
 885 890 895
 Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
 900 905 910
 Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
 915 920 925
 Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
 930 935 940
 Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
 945 950 955 960
 Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
 965 970 975
 Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
 980 985 990
 Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
 995 1000 1005
 Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
 1010 1015 1020
 Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile
 1025 1030 1035
 Lys Gln Tyr
 1040

<210> 54
 <211> 1059
 <212> PRT
 <213> Homo sapiens

<400> 54

```

Met Lys Glu Ser Ser Leu Gln Asn Ser Ser Cys Ser Leu Gly Lys Glu
1              5              10              15
Thr Lys Lys Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile
              20              25              30
Phe Leu Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe
              35              40              45
Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile
              50              55              60
Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly
65              70              75              80
Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile
              85              90              95
Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu
              100             105             110
Asn His Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln
              115             120             125
Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn
              130             135             140
Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser
145             150             155             160
Gly Leu Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile
              165             170             175
Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn
              180             185             190
Leu Tyr Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr
              195             200             205
Asn Ile Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu
              210             215             220
Ser Leu Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser
225             230             235             240
Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser
              245             250             255
Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser
              260             265             270
Gly Asn Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys
              275             280             285

```

Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu
 290 295 300
 Thr Gln Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile
 305 310 315 320
 Asn Ala Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu
 325 330 335
 Glu Phe Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr
 340 345 350
 Met Leu Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys
 355 360 365
 Gly Ser Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu
 370 375 380
 Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu
 385 390 395 400
 Arg Glu Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr
 405 410 415
 Ile Asn Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe
 420 425 430
 Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile
 435 440 445
 Ser Pro Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser
 450 455 460
 Phe Gln Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp
 465 470 475 480
 Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln
 485 490 495
 Cys Ala Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe
 500 505 510
 Phe Ile Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu
 515 520 525
 Asn Leu Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe
 530 535 540
 Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu
 545 550 555 560
 Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val
 565 570 575
 Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr
 580 585 590
 His His Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn
 595 600 605
 Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu

610 615 620
 Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile
 625 630 635 640
 Leu Trp Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu
 645 650 655
 Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile
 660 665 670
 Pro Asn Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His
 675 680 685
 Ile Asn Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln
 690 695 700
 Phe Pro Arg Leu Glu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe
 705 710 715 720
 Leu Thr Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu
 725 730 735
 Leu Ser His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu
 740 745 750
 Val Ser Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr
 755 760 765
 Ile Asn Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met
 770 775 780
 Leu Glu Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp
 785 790 795 800
 Phe Arg Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu
 805 810 815
 Val Asp Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile
 820 825 830
 Val Ser Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile
 835 840 845
 Leu Phe Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala
 850 855 860
 Leu Ala His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val
 865 870 875 880
 Cys Leu Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr
 885 890 895
 Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr
 900 905 910
 Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp
 915 920 925
 Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu
 930 935 940
 Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr

945 950 955 960
 Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr
 965 970 975
 Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val
 980 985 990
 Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu
 995 1000 1005
 Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro
 1010 1015 1020
 Asp Asn Pro Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn
 1025 1030 1035
 Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val
 1040 1045 1050
 Asp Ser Ile Lys Gln Tyr
 1055

<210> 55
 <211> 3220
 <212> DNA
 <213> murine

<400> 55
 attcagagtt ggatgttaag agagaaacaa acgttttacc ttcctttgtc tatagaacat 60
 ggaaaacatg cccctcagtc catggattct gacgtgcttt tgtctgctgt cctctggaac 120
 cagtgccatc ttccataaag cgaactattc cagaagctat ccttgtgacg agataaggca 180
 caactccctt gtgattgcag aatgcaacca tcgtcaactg catgaagttc cccaaactat 240
 aggcaagtat gtgacaaaca tagacttgct agacaatgcc attacacata taacgaaaga 300
 gtcctttcaa aagctgcaaa acctcactaa aatcgatctg aaccacaatg ccaaacaaca 360
 gcacccaaat gaaaataa'aa atgggtatgaa tattacagaa ggggcacttc tcagcctaag 420
 aaatctaaca gttttactgc tggaagacaa ccagttatat actatacctg ctggggtgcc 480
 tgagtctttg aaagaactta gcctaattca aaacaatata tttcaggtaa ctaaaaacaa 540
 cacttttggg cttaggaact tggaaagact ctatttgggc tggaactgct attttaaatg 600
 taatcaaacc ttttaaggtag aagatggggc atttaaaaat cttatacact tgaaggtact 660
 ctcattatct ttcaataacc ttttctatgt gcccccaaa ctaccaagtt ctctaaggaa 720
 actttttctg agtaatgcca aaatcatgaa catcactcag gaagacttca aaggactgga 780
 aaatttaaca ttactagatc tgagtggaaa ctgtccaagg tgttacaatg ctccatttcc 840
 ttgcacacct tgcaaggaaa actcatccat ccacatacat cctctggctt ttcaaagtct 900
 caccacaact ctctatctaa acctttccag cacttccctc aggacgattc cttctacctg 960
 gtttgaaaat ctgtcaaadc tgaaggaaact ccatcttgaa ttcaactatt tagttcaaga 1020

aattgcctcg ggggcatttt taacaaaact acccagttta caaatccttg atttgcctt 1080
caactttcaa tataaggaat atttacaatt tattaatatt tcctcaaatt tctctaagct 1140
tcgttctctc aagaagttgc acttaagagg ctatgtgttc cgagaactta aaaagaagca 1200
tttcgagcat ctccagagtc ttccaaactt ggcaaccatc aacttgggca ttaactttat 1260
tgagaaaatt gatttcaaag ctttccagaa tttttccaaa ctgcaggtta tctattttatc 1320
aggaaatcgc atagcatctg tattagatgg tacagattat tcctcttggc gaaatcgtct 1380
tcggaaacct ctctcaacag acgatgatga gtttgatcca cacgtgaatt tttaccatag 1440
caccaaactt ttaataaagc cacagtgtac tgcttatggc aaggccttgg atttaagttt 1500
gaacaatatt ttcattattg ggaaaagcca atttgaaggt tttcaggata tcgcctgctt 1560
aaatctgtcc ttcaatgcca atactcaagt gtttaaatggc acagaattct cctccatgcc 1620
ccacattaaa tatttggatt taaccaacaa cagactagac ttgatgata acaatgcttt 1680
cagtgatctt cacgatctag aagtgtctga cctgagccac aatgcacact atttcagtat 1740
agcaggggta acgcaccgtc taggatttat ccagaactta ataaacctca ggggtgttaaa 1800
cctgagccac aatggcattt acaccctcac agaggaaagt gagctgaaaa gcatctcact 1860
gaaagaattg gttttcagtg gaaatcgtct tgaccatttg tggaatgcaa atgatggcaa 1920
atactggtcc attttttaaaa gtctccagaa ttgatacgc ctggacttat catacataa 1980
ccttcaacaa atcccaaag gagcattcct caatttgcct cagagcctcc aagagttact 2040
tatcagtggg aacaaattac gtttctttaa ttggacatta ctccagtatt ttccctcacct 2100
tcacttgctg gatttatcga gaaatgagct gtattttcta cccaattgcc tatctaagtt 2160
tgcacattcc ctggagacac tgctactgag ccataatcat ttctctcacc taccctctgg 2220
cttctctccc gaagccagga atctggtgca cctggatcta agtttcaaca caataaagat 2280
gatcaataaa tcctccctgc aaaccaagat gaaaacgaac ttgtctattc tggagctaca 2340
tgggaactat tttgactgca cgtgtgacat aagtgatatt cgaagctggc tagatgaaaa 2400
tctgaatatc acaattccta aattggtaaa tgttatatgt tccaatcctg gggatcaaaa 2460
atcaaagagt atcatgagcc tagatctcac gacttgtgta tcggatacca ctgcagctgt 2520
cctgtttttc ctacattcc ttaccacctc catggttatg ttggctgctc tggttcacca 2580
cctgttttac tgggatgttt ggtttatcta tcacatgtgc tctgctaagt taaaaggcta 2640
caggacttca tccacatccc aaactttcta tgatgcttat atttcttatg acaccaaaga 2700
tgcatctgtt actgactggg taatcaatga actgcgctac caccttgaag agagtgaaga 2760
caaaagtgtc ctcttttgtt tagaggagag ggattgggat ccaggattac ccatcattga 2820
taacctcatg cagagcataa accagagcaa gaaaacaatc tttgttttaa ccaagaaata 2880

tgccaagagc tggaacttta aaacagcttt ctacttggcc ttgcagaggc taatggatga 2940
 gaacatggat gtgattatth tcatcctcct ggaaccagtg ttacagtact cacagtacct 3000
 gaggcttcgg cagaggatct gtaagagctc catcctccag tggcccaaca atcccaaagc 3060
 agaaaacttg ttttggcaaa gtctgaaaaa tgtggtcttg actgaaaatg attcacggta 3120
 tgacgatttg tacattgatt ccattaggca atactagtga tgggaagtca cgactctgcc 3180
 atcataaaaa cacacagctt ctccttacia tgaaccgaat 3220

<210> 56
 <211> 3220
 <212> DNA
 <213> murine

<400> 56
 attcagagtt ggatgttaag agagaaacaa acgtttttacc ttcctttgtc tatagaacat 60
 ggaaaacatg cccctcagc catggattct gacgtgcttt tgtctgctgt cctctggaac 120
 cagtgccatc ttccataaag cgaactattc cagaagctat ccttgtgacg agataaggca 180
 caactccctt gtgattgcag aatgcaacca tcgtcaactg catgaagtcc cccaaactat 240
 aggcaagtat gtgacaaaca tagacttgtc agacaatgcc attacacata taacgaaaga 300
 gtcctttcaa aagctgcaaa acctcactaa aatcgatctg aaccacaatg ccaaacaaca 360
 gcacccaaat gaaaataaaa atggtatgaa tattacagaa ggggcacttc tcagcctaag 420
 aaatctaaca gttttactgc tggaagacaa ccagttatat actatacctg ctgggttgcc 480
 tgagtctttg aaagaactta gcctaattca aaacaatata tttcaggtaa ctaaaaaaca 540
 cacttttggg cttaggaact tggaaagact ctatttgggc tggaaactgct attttaaatg 600
 taatcaaacc tttaaggtag aagatggggc atttaaaaat cttatacact tgaaggtagt 660
 ctattatctt ttcaataacc ttttctatgt gcccccaaa ctaccaagtt ctctaaggaa 720
 actttttctg agtaatgcca aaatcatgaa catcactcag gaagacttca aaggactgga 780
 aaatttaaca ttactagatc tgagtggaaa ctgtccaagg tgttacaatg ctccatttcc 840
 ttgcacacct tgcaaggaaa actcatccat ccacatacat cctctggctt ttcaaagtct 900
 caccacactt ctctatctaa acctttccag cacttccctc aggacgattc cttctacctg 960
 gtttgaaaat ctgtcaaact tgaaggaaact ccatcttgaa ttcaactatt tagttcaaga 1020
 aattgcctcg ggggcatttt taacaaaact acccagttta caaatccttg atttgtcctt 1080
 caactttcaa tataaggaaat atttacaatt tattaatatt tcctcaaatt tctctaagct 1140
 tcgttctctc aagaagttgc acttaagagg ctatgtgttc cgagaactta aaaagaagca 1200
 tttcgagcat ctccagagtc ttccaaactt ggcaaccatc aacttgggca ttaactttat 1260

tgagaaaatt	gatttcaaag	ctttccagaa	tttttccaaa	ctcgacgtta	tctatttatc	1320
aggaaatcgc	atagcatctg	tattagatgg	tacagattat	tcctcttggc	gaaatcgtct	1380
tcggaaacct	ctctcaacag	acgatgatga	gtttgatcca	cacgtgaatt	tttaccatag	1440
caccaaacct	ttaataaagc	cacagtgtac	tgcttatggc	aaggccttgg	atttaagttt	1500
gaacaatatt	ttcattattg	ggaaaagcca	atltgaaggt	tttcaggata	tcgcctgctt	1560
aaatctgtcc	ttcaatgcc	atactcaagt	gtttaatggc	acagaattct	cctccatgcc	1620
ccacattaaa	tatttggatt	taaccaacaa	cagactagac	tttgatgata	acaatgcttt	1680
cagtgatctt	cacgatctag	aagtgtctga	cctgagccac	aatgcacact	atttcagtat	1740
agcaggggta	acgcaccgtc	taggatttat	ccagaactta	ataaacctca	gggtgttaaa	1800
cctgagccac	aatggcattt	acaccctcac	agaggaaagt	gagctgaaaa	gcctctcact	1860
gaaagaattg	gttttcagt	gaaatcgtct	tgaccatttg	tggaatgcaa	atgatggcaa	1920
atactggctc	attttttaaa	gtctccagaa	tttgatacgc	ctggacttat	catacataaa	1980
ccttcaacaa	atcccaaagt	gagcattcct	caatttgcct	cagagcctcc	aagagttact	2040
tatcagtggg	aacaaattac	gtttctttta	ttggacatta	ctccagtatt	ttcctcacct	2100
tcacttgctg	gatttatcga	gaaatgagct	gtattttcta	cccaattgcc	tatctaagtt	2160
tgacattccc	ctggagacac	tgctactgag	ccataatcat	ttctctcacc	taccctctgg	2220
cttcctctcc	gaagccagga	atctgggtgca	cctggatcta	agtttcaaca	caataaagat	2280
gatcaataaa	tcctccctgc	aaaccaagat	gaaaacgaac	ttgtctattc	tggagctaca	2340
tgggaactat	tttgactgca	cgtgtgacat	aagtgtattt	cgaagctggc	tagatgaaaa	2400
tctgaatatc	acaattccta	aattggtaaa	tggtatatgt	tccaatcctg	gggatcaaaa	2460
atcaaagagt	atcatgagcc	tagatctcac	gacttgtgta	tcggatacca	ctgcagctgt	2520
cctgtttttc	ctcacattcc	ttaccacctc	catggttatg	ttggctgctc	tggttcacca	2580
cctgtttttac	tgggatgttt	ggtttatcta	tcacatgtgc	tctgctaagt	taaaaggcta	2640
caggacttca	tccacatccc	aaactttcta	tgatgcttat	atttcttatg	acaccaaaga	2700
tgcatctgtt	actgactggg	taatcaatga	actgcgctac	caccttgaag	agagtgaaga	2760
caaaagtgtc	ctcctttgtt	tagaggagag	ggattgggat	ccaggattac	ccatcattga	2820
taacctcatg	cagagcataa	accagagcaa	gaaaacaatc	tttgttttaa	ccaagaaata	2880
tgccaagagc	tggaaactta	aaacagcttt	ctacttggcc	ttgcagaggc	taatggatga	2940
gaacatggat	gtgattatlt	tcctcctcct	ggaaccagt	ttacagtact	cacagtacct	3000
gaggcttcgg	cagaggatct	gtaagagctc	catcctccag	tggcccaaca	atcccaaagc	3060
agaaaacttg	ttttggcaaa	gtctgaaaaa	tgtggctctt	actgaaaatg	attcacggta	3120
tgacgatttg	tacattgatt	ccattaggca	atactagtga	tgggaagtca	cgactctgcc	3180

atcataaaaa cacacagctt ctccttaca tgaaccgaat

3220

<210> 57
 <211> 1032
 <212> PRT
 <213> murine

<400> 57

Met Glu Asn Met Pro Pro Gln Ser Trp Ile Leu Thr Cys Phe Cys Leu
 1 5 10 15

Leu Ser Ser Gly Thr Ser Ala Ile Phe His Lys Ala Asn Tyr Ser Arg
 20 25 30

Ser Tyr Pro Cys Asp Glu Ile Arg His Asn Ser Leu Val Ile Ala Glu
 35 40 45

Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr
 50 55 60

Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys
 65 70 75 80

Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His
 85 90 95

Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile
 100 105 110

Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu
 115 120 125

Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu
 130 135 140

Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn
 145 150 155 160

Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn
 165 170 175

Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe
 180 185 190

Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu
 195 200 205

Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
 210 215 220

Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu
 225 230 235 240

Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr
 245 250 255

Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His
 260 265 270

Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn
275 280 285

Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn
290 295 300

Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln
305 310 315 320

Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile
325 330 335

Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile
340 345 350

Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His
355 360 365

Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His
370 375 380

Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe
385 390 395 400

Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp
405 410 415

Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr
420 425 430

Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp
435 440 445

Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro
450 455 460

Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser
465 470 475 480

Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln
485 490 495

Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe
500 505 510

Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu
515 520 525

Thr Asn Asn Arg Leu Asp Phe Asp Asp Asn Asn Ala Phe Ser Asp Leu
530 535 540

His Asp Leu Glu Val Leu Asp Leu Ser His Asn Ala His Tyr Phe Ser
545 550 555 560

Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn
565 570 575

Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu
580 585 590

Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly

595	600	605
Asn Arg Leu Asp His Leu Trp	Asn Ala Asn Asp Gly Lys Tyr Trp Ser	
610	615	620
Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn		
625	630	635
640		
Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser		
645	650	655
Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp		
660	665	670
Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg		
675	680	685
Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser		
690	695	700
Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser		
705	710	715
720		
Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe		
725	730	735
Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys		
740	745	750
Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr		
755	760	765
Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile		
770	775	780
Thr Ile Pro Lys Leu Val Asn Val Ile Cys Ser Asn Pro Gly Asp Gln		
785	790	795
800		
Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp		
805	810	815
Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met		
820	825	830
Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp		
835	840	845
Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser		
850	855	860
Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys		
865	870	875
880		
Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu		
885	890	895
Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp		
900	905	910
Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn		
915	920	925
Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser		

930 935 940
 Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp
 945 950 955 960
 Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln
 965 970 975
 Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile
 980 985 990
 Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser
 995 1000 1005
 Leu Lys Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asp Asp
 1010 1015 1020
 Leu Tyr Ile Asp Ser Ile Arg Gln Tyr
 1025 1030

<210> 58
 <211> 1032
 <212> PRT
 <213> murine

<400> 58

Met Glu Asn Met Pro Pro Gln Ser Trp Ile Leu Thr Cys Phe Cys Leu
 1 5 10 15
 Leu Ser Ser Gly Thr Ser Ala Ile Phe His Lys Ala Asn Tyr Ser Arg
 20 25 30
 Ser Tyr Pro Cys Asp Glu Ile Arg His Asn Ser Leu Val Ile Ala Glu
 35 40 45
 Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr
 50 55 60
 Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys
 65 70 75 80
 Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His
 85 90 95
 Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile
 100 105 110
 Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu
 115 120 125
 Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu
 130 135 140
 Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn
 145 150 155 160
 Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn
 165 170 175
 Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe
 180 185 190

Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu
 195 200 205
 Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
 210 215 220
 Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu
 225 230 235 240
 Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr
 245 250 255
 Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His
 260 265 270
 Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn
 275 280 285
 Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn
 290 295 300
 Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln
 305 310 315 320
 Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile
 325 330 335
 Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile
 340 345 350
 Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His
 355 360 365
 Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His
 370 375 380
 Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe
 385 390 395 400
 Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp
 405 410 415
 Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr
 420 425 430
 Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp
 435 440 445
 Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro
 450 455 460
 Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser
 465 470 475 480
 Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln
 485 490 495
 Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe
 500 505 510
 Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu

Thr	Asn	Asn	Arg	Leu	Asp	Phe	Asp	Asp	Asn	Asn	Ala	Phe	Ser	Asp	Leu
530						535					540				
His	Asp	Leu	Glu	Val	Leu	Asp	Leu	Ser	His	Asn	Ala	His	Tyr	Phe	Ser
545					550					555					560
Ile	Ala	Gly	Val	Thr	His	Arg	Leu	Gly	Phe	Ile	Gln	Asn	Leu	Ile	Asn
				565					570						575
Leu	Arg	Val	Leu	Asn	Leu	Ser	His	Asn	Gly	Ile	Tyr	Thr	Leu	Thr	Glu
			580					585					590		
Glu	Ser	Glu	Leu	Lys	Ser	Ile	Ser	Leu	Lys	Glu	Leu	Val	Phe	Ser	Gly
		595					600					605			
Asn	Arg	Leu	Asp	His	Leu	Trp	Asn	Ala	Asn	Asp	Gly	Lys	Tyr	Trp	Ser
610						615					620				
Ile	Phe	Lys	Ser	Leu	Gln	Asn	Leu	Ile	Arg	Leu	Asp	Leu	Ser	Tyr	Asn
625					630					635					640
Asn	Leu	Gln	Gln	Ile	Pro	Asn	Gly	Ala	Phe	Leu	Asn	Leu	Pro	Gln	Ser
				645					650						655
Leu	Gln	Glu	Leu	Leu	Ile	Ser	Gly	Asn	Lys	Leu	Arg	Phe	Phe	Asn	Trp
			660					665						670	
Thr	Leu	Leu	Gln	Tyr	Phe	Pro	His	Leu	His	Leu	Leu	Asp	Leu	Ser	Arg
			675				680					685			
Asn	Glu	Leu	Tyr	Phe	Leu	Pro	Asn	Cys	Leu	Ser	Lys	Phe	Ala	His	Ser
690						695					700				
Leu	Glu	Thr	Leu	Leu	Leu	Ser	His	Asn	His	Phe	Ser	His	Leu	Pro	Ser
705					710					715					720
Gly	Phe	Leu	Ser	Glu	Ala	Arg	Asn	Leu	Val	His	Leu	Asp	Leu	Ser	Phe
				725					730					735	
Asn	Thr	Ile	Lys	Met	Ile	Asn	Lys	Ser	Ser	Leu	Gln	Thr	Lys	Met	Lys
			740					745						750	
Thr	Asn	Leu	Ser	Ile	Leu	Glu	Leu	His	Gly	Asn	Tyr	Phe	Asp	Cys	Thr
		755					760						765		
Cys	Asp	Ile	Ser	Asp	Phe	Arg	Ser	Trp	Leu	Asp	Glu	Asn	Leu	Asn	Ile
770						775					780				
Thr	Ile	Pro	Lys	Leu	Val	Asn	Val	Ile	Cys	Ser	Asn	Pro	Gly	Asp	Gln
785					790					795					800
Lys	Ser	Lys	Ser	Ile	Met	Ser	Leu	Asp	Leu	Thr	Thr	Cys	Val	Ser	Asp
				805					810					815	
Thr	Thr	Ala	Ala	Val	Leu	Phe	Phe	Leu	Thr	Phe	Leu	Thr	Thr	Ser	Met
				820				825						830	
Val	Met	Leu	Ala	Ala	Leu	Val	His	Leu	Phe	Tyr	Trp	Asp	Val	Trp	
		835					840				845				
Phe	Ile	Tyr	His	Met	Cys	Ser	Ala	Lys	Leu	Lys	Gly	Tyr	Arg	Thr	Ser

850 855 860
 Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys
 865 870 875 880
 Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu
 885 890 895
 Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp
 900 905 910
 Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn
 915 920 925
 Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser
 930 935 940
 Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp
 945 950 955 960
 Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln
 965 970 975
 Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile
 980 985 990
 Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser
 995 1000 1005
 Leu Lys Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asp Asp
 1010 1015 1020
 Leu Tyr Ile Asp Ser Ile Arg Gln Tyr
 1025 1030

<210> 59
 <211> 1032
 <212> PRT
 <213> murine

<400> 59

Met Glu Asn Met Pro Pro Gln Ser Trp Ile Leu Thr Cys Phe Cys Leu
 1 5 10 15
 Leu Ser Ser Gly Thr Ser Ala Ile Phe His Lys Ala Asn Tyr Ser Arg
 20 25 30
 Ser Tyr Pro Cys Asp Glu Ile Arg His Asn Ser Leu Val Ile Ala Glu
 35 40 45
 Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr
 50 55 60
 Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys
 65 70 75 80
 Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His
 85 90 95
 Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile
 100 105 110

Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu
 115 120 125
 Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu
 130 135 140
 Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn
 145 150 155 160
 Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn
 165 170 175
 Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe
 180 185 190
 Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu
 195 200 205
 Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
 210 215 220
 Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu
 225 230 235 240
 Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr
 245 250 255
 Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His
 260 265 270
 Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn
 275 280 285
 Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn
 290 295 300
 Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln
 305 310 315 320
 Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile
 325 330 335
 Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile
 340 345 350
 Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His
 355 360 365
 Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His
 370 375 380
 Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe
 385 390 395 400
 Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp
 405 410 415
 Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr
 420 425 430
 Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp

435 440 445
 Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro
 450 455 460
 Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser
 465 470 475 480
 Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln
 485 490 495
 Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe
 500 505 510
 Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu
 515 520 525
 Thr Asn Asn Arg Leu Asp Phe Asp Asp Asn Asn Ala Phe Ser Asp Leu
 530 535 540
 His Asp Leu Glu Val Leu Asp Leu Ser His Asn Ala His Tyr Phe Ser
 545 550 555 560
 Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn
 565 570 575
 Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu
 580 585 590
 Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly
 595 600 605
 Asn Arg Leu Asp His Leu Trp Asn Ala Asn Asp Gly Lys Tyr Trp Ser
 610 615 620
 Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn
 625 630 635 640
 Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser
 645 650 655
 Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp
 660 665 670
 Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg
 675 680 685
 Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser
 690 695 700
 Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser
 705 710 715 720
 Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe
 725 730 735
 Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys
 740 745 750
 Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr
 755 760 765
 Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile

770 775 780
 Thr Ile Pro Lys Leu Val Asn Val Ile Cys Ser Asn Pro Gly Asp Gln
 785 790 795 800
 Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp
 805 810 815
 Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met
 820 825 830
 Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp
 835 840 845
 Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser
 850 855 860
 Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys
 865 870 875 880
 Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu
 885 890 895
 Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp
 900 905 910
 Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn
 915 920 925
 Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser
 930 935 940
 Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp
 945 950 955 960
 Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln
 965 970 975
 Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile
 980 985 990
 Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser
 995 1000 1005
 Leu Lys Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asp Asp
 1010 1015 1020
 Leu Tyr Ile Asp Ser Ile Arg Gln Tyr
 1025 1030

<210> 60

<211> 3352

<212> DNA

<213> Homo sapiens

<400> 60

aggctggtat aaaaatctta cttcctctat tctctgagcc gctgctgccc ctgtgggaag 60

ggacctcgag tgtgaagcat ccttccctgt agctgctgtc cagtctgccc gccagaccct 120

ctggagaagc ccctgcccc cagcatgggt ttctgccgca gcgccctgca cccgctgtct 180

ctcctgggtgc	aggccatcat	gctggccatg	accctggccc	tgggtacctt	gcctgccttc	240
ctaccctgtg	agctccagcc	ccacggcctg	gtgaactgca	actggctgtt	cctgaagtct	300
gtgccccact	tctccatggc	agcaccocgt	ggcaatgtca	ccagcctttc	cttgtcctcc	360
aaccgcatcc	accacctcca	tgattctgac	tttgcccacc	tgcccagcct	gcggcatctc	420
aacctcaagt	ggaactgccc	gccggttggc	ctcagcccca	tgcacttccc	ctgccacatg	480
accatcgagc	ccagcacctt	cttggctgtg	cccaccctgg	aagagctaaa	cctgagctac	540
aacaacatca	tgactgtgcc	tgcgctgccc	aaatccctca	tatccctgtc	cctcagccat	600
accaacatcc	tgatgctaga	ctctgccagc	ctcgccggcc	tgcatgccct	gcgcttccta	660
ttcatggacg	gcaactgtta	ttacaagaac	ccctgcaggc	aggcactgga	ggtggccccg	720
ggtgccctcc	ttggcctggg	caacctcacc	cacctgtcac	tcaagtacaa	caacctcact	780
gtggtgcccc	gcaacctgcc	ttccagcctg	gagtatctgc	tgttgtccta	caaccgcata	840
gtcaaactgg	cgctgagga	cctggccaat	ctgaccgccc	tgcggtgtgt	cgatgtgggc	900
ggaaattgcc	gccgctgcca	ccacgctccc	aaccctcgca	tggagtgcgc	tcgtcacttc	960
ccccagctac	atcccgatac	cttcagccac	ctgagccgtc	ttgaaggcct	ggtgttgaag	1020
gacagttctc	tctcctggct	gaatgccagt	tggttcctgt	ggctgggaaa	cctccgagtg	1080
ctggacctga	gtgagaactt	cctctacaaa	tgcatcacta	aaaccaaggc	cttccagggc	1140
ctaacacagc	tgcgcaagct	taacctgtcc	ttcaattacc	aaaagagggg	gtcctttgcc	1200
cacctgtctc	tggccccttc	cttcgggagc	ctggctgccc	tgaaggagct	ggacatgcac	1260
ggcatcttct	tcgctcact	cgatgagacc	acgctccggc	cactggcccc	cctgcccata	1320
ctccagactc	tgcgctctga	gatgaacttc	atcaaccagg	cccagctcgg	catcttcagg	1380
gccttccctg	gcctgcgcta	cgtggacctg	tcggacaacc	gcatcagcgg	agcttcggag	1440
ctgacagcca	ccatggggga	ggcagatgga	ggggagaagg	tctggctgca	gcctggggac	1500
cttgctccgg	cccagtgga	cactcccagc	tctgaagact	tcaggcccaa	ctgcagcacc	1560
ctcaacttca	ccttgatct	gtcacggaac	aacctgggtg	ccgtgcagcc	ggagatgttt	1620
gccagctct	cgcacctgca	gtgcctgcgc	ctgagccaca	actgcatctc	gcaggcagtc	1680
aatggctccc	agttcctgcc	gctgaccggg	ctgcaggtgc	tagacctgtc	ccgcaataag	1740
ctggacctct	accacgagca	ctcattcacg	gagctaccgc	gactggaggc	cctggacctc	1800
agctacaaca	gccagccctt	tggcatgcag	ggcgtggggc	acaacttcag	cttcgtggct	1860
cacctgcgca	ccctgcgcca	cctcagcctg	gcccacaaca	acatccacag	ccaagtgtcc	1920
cagcagctct	gcagtacgtc	gctgcggggc	ctggacttca	gcggcaatgc	actgggccat	1980
atgtggggccg	aggagacct	ctatctgcac	ttcttccaag	gcctgagcgg	tttgatctgg	2040
ctggacttgt	cccagaaccg	cctgcacacc	ctcctgcccc	aaacctgcg	caacctcccc	2100

aagagcctac aggtgctgcg tctccgtgac aattacctgg ccttctttaa gtggtggagc 2160
ctccacttcc tgcccaaact ggaagtccctc gacctggcag gaaaccggct gaaggccctg 2220
accaatggca gcctgcctgc tggcaccggtg ctccggaggc tggatgtcag ctgcaacagc 2280
atcagcttcg tggcccccggt cttcttttcc aaggccaagg agctgcgaga gctcaacctt 2340
agcgccaacg cctcaagac agtggaccac tcttggtttg ggccctggc gagtgccctg 2400
caaatactag atgtaagcgc caacctctg cactgcgcct gtggggcggc ctttatggac 2460
ttctgctgg aggtgcaggc tgccgtgccc ggtctgccc gccgggtgaa gtgtggcagt 2520
ccgggccagc tccagggcct cagcatcttt gcacaggacc tgcgcctctg cctggatgag 2580
gccctctcct gggactgttt cggcctctcg ctgctggctg tggctctggg cctgggtgtg 2640
cccatgctgc atcacctctg tggctgggac ctctggtact gcttccacct gtgcctggcc 2700
tggcttccct ggcggggggtg gcaaagtggg cgagatgagg atgccctgcc ctacgatgcc 2760
ttcgtggtct tcgacaaaac gcagagcgca gtggcagact ggggtgacaa cgagcttcgg 2820
gggcagctgg aggagtgcg tgggcgctgg gcactccgcc tgtgcctgga ggaacgcgac 2880
tggctgcctg gcaaaacctt ctttgagaac ctgtgggcct cggctctatgg cagccgcaag 2940
acgctgtttg tgetggccca cacggaccgg gtcagtggc tcttgccgc cagcttctg 3000
ctggcccagc agcgctgct ggaggaccgc aaggacgtcg tggctgctgt gatcctgagc 3060
cctgacggcc gcgctcccc ctacgtgcgg ctgcgccagc gcctctgcc ccagagtgtc 3120
ctcctctggc cccaccagcc cagtggctag cgcagcttct gggcccagct gggcatggcc 3180
ctgaccaggg acaaccacca cttctataac cggaacttct gccagggacc cacggccgaa 3240
tagccgtgag ccggaatcct gcacgggtgcc acctccacac tcacctcacc tctgcctgcc 3300
tggctgacc ctcccctgct cgcctccctc accccacacc tgacacagag ca 3352

<210> 61

<211> 3257

<212> DNA

<213> Homo sapiens

<400> 61

ccgtgctgc cctgtggga agggacctcg agtgtgaagc atccttccct gtagctgctg 60
tccagtctgc ccgccagacc ctctggagaa gccctgccc ccagcatgg gtttctgccc 120
cagcgccctg caccgctgt ctctcctggt gcaggccatc atgtggcca tgacctggc 180
cctgggtacc ttgctgcct tcctacctg tgagctccag cccacggcc tggatgaactg 240
caactggctg ttctgaagt ctgtgcccc cttctccatg gcagcaccgc gtggcaatgt 300
caccagcctt tcttgtcct ccaaccgat ccaccacctc catgattctg actttgccc 360

cctgcccagc	ctgcggcatc	tcaacctcaa	gtggaactgc	ccgccgggtg	gcctcagccc	420
catgcacttc	ccctgccaca	tgaccatcga	gccagcacc	ttcttggtg	tgcccaccct	480
ggaagagcta	aacctgagct	acaacaacat	catgactgtg	cctgcgctgc	ccaaatccct	540
catatccctg	tcctcagcc	ataccaacat	cctgatgcta	gactctgcca	gcctcgccgg	600
cctgcatgcc	ctgcgcttcc	tattcatgga	eggcaactgt	tattacaaga	acccctgcag	660
gcaggcactg	gaggtggccc	cggtgcccct	ccttggcctg	ggcaacctca	cccacctgtc	720
actcaagtac	aacaacctca	ctgtggtgcc	ccgcaacctg	ccttcagcc	tggagtatct	780
gctgttgtcc	tacaaccgca	tcgtcaaact	ggcgctgag	gacctggcca	atctgaccgc	840
cctgcgtgtg	ctcgatgtgg	gcggaaattg	ccgccgtgc	gaccacgctc	ccaaccctg	900
catggagtgc	cctcgtcact	tccccagct	acatcccgat	accttcagcc	acctgagccg	960
tcttgaaggc	ctggtgttga	aggacagttc	tctctcctgg	ctgaatgcca	gttgggttccg	1020
tgggctggga	aacctccgag	tgctggacct	gagtgagaac	ttcctctaca	aatgcatcac	1080
taaaaccaag	gccttcaggg	gcctaacaca	gctgcgcaag	cttaacctgt	ccttcaatta	1140
ccaaaagagg	gtgtcctttg	cccacctgtc	tctggcccct	tccttcggga	gcctggctgc	1200
cctgaaggag	ctggacatgc	acggcatctt	cttcgcgtca	ctcgatgaga	ccacgctccg	1260
gccactggcc	cgctgccc	tgctccagac	tctgcgtctg	cagatgaact	tcatcaacca	1320
ggcccagctc	ggcatcttca	gggccttccc	tggcctgcgc	tacgtggacc	tgctggacaa	1380
ccgcatcagc	ggagcttcgg	agctgacagc	caccatgggg	gaggcagatg	gaggggagaa	1440
ggtctggctg	cagcctgggg	accttgctcc	ggccccagtg	gacactccca	gctctgaaga	1500
cttcaggccc	aactgcagca	ccctcaactt	caccttggat	ctgtcacgga	acaacctggt	1560
gacctgagc	ccggagatgt	ttgcccagct	ctgcacactg	cagtgcctgc	gcctgagcca	1620
caactgcac	tcgcaggcag	tcaatggctc	ccagttcctg	ccgctgaccg	gtctgcaggt	1680
gctagacctg	tcccacaata	agctggacct	ctaccacgag	cactcattca	cggagctacc	1740
acgactggag	gccctggacc	tcagctacaa	cagccagccc	tttggcatgc	agggcggtgg	1800
ccacaacttc	agcttcgtgg	ctcacctgcg	cacctgcgc	cacctcagcc	tggcccacaa	1860
caacatccac	agccaagtgt	cccagcagct	ctgcagtacg	tcgctgcggg	ccctggactt	1920
cagcggcaat	gcactgggccc	atatgtgggc	cgaggagac	ctctatctgc	acttcttcca	1980
aggcctgagc	ggtttgatct	ggctggactt	gtcccagaac	cgctgcaca	ccctcctgcc	2040
ccaaaccctg	cgcaacctcc	ccaagagcct	acaggtgctg	cgtctccgtg	acaattacct	2100
ggccttcttt	aagtgttga	gcctccactt	cctgcccac	ctggaagtcc	tcgacctggc	2160
aggaaaccag	ctgaaggccc	tgaccaatgg	cagcctgcct	gctggcacc	ggctccggag	2220
gctggatgtc	agctgcaaca	gcacagctt	cgtggcccc	ggcttctttt	ccaaggccaa	2280

ggagctgcga gagctcaacc ttagcgccaa cgccctcaag acagtggacc actcctgggtt 2340
 tgggcccctg gcgagtgcc tgcaaatact agatgtaagc gccaaccctc tgcactgcgc 2400
 ctgtggggcg gcctttatgg acttcctgct ggaggtgcag gctgccgtgc ccggtctgcc 2460
 cagccgggtg aagtgtggca gtccgggcca gctccagggc ctcagcatct ttgcacagga 2520
 cctgcgcctc tgcttgatg aggcctctc ctgggactgt ttgcctctc cgctgctggc 2580
 tgtggctctg ggctgggtg tgcccatgct gcatcacctc tgtggctggg acctctggta 2640
 ctgcttcac ctgtgcctgg cctggcttcc ctggcggggg cggcaaagtg ggcgagatga 2700
 ggatgccctg cctacgatg ccttcgtggt cttcgacaaa acgcagagcg cagtggcaga 2760
 ctgggtgtac aacgagcttc gggggcagct ggaggagtgc cgtgggcgct gggcactccg 2820
 cctgtgcctg gaggaacgcg actggctgcc tggcaaaacc ctctttgaga acctgtgggc 2880
 ctcggtctat ggcagccgca agacgtgtt tgtgctggcc cacacggacc gggtcagtgg 2940
 tctcttgccg gccagcttcc tgctggccca gcagcgctg ctggaggacc gcaaggacgt 3000
 cgtggtgctg gtgatcctga gccctgacgg ccgccgctcc cgctacgtgc ggctgcgcca 3060
 gcgcctctgc cgccagagtg tctcctctg gcccaccag ccagtggtc agcgcagctt 3120
 ctgggcccag ctgggcatgg cctgaccag ggacaaccac cacttctata accggaactt 3180
 ctgccagga cccacggccg aatagccgtg agccggaatc ctgcacggtg ccacctccac 3240
 actcacctca cctctgc 3257

<210> 62
 <211> 1032
 <212> PRT
 <213> Homo sapiens

<400> 62

Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
 1 5 10 15
 Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
 20 25 30
 Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
 35 40 45
 Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
 50 55 60
 Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
 65 70 75 80
 Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
 85 90 95
 Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met

Thr	Ile	Glu	Pro	Ser	Thr	Phe	Leu	Ala	Val	Pro	Thr	Leu	Glu	Glu	Leu
		115					120					125			
Asn	Leu	Ser	Tyr	Asn	Asn	Ile	Met	Thr	Val	Pro	Ala	Leu	Pro	Lys	Ser
	130					135					140				
Leu	Ile	Ser	Leu	Ser	Leu	Ser	His	Thr	Asn	Ile	Leu	Met	Leu	Asp	Ser
145					150					155					160
Ala	Ser	Leu	Ala	Gly	Leu	His	Ala	Leu	Arg	Phe	Leu	Phe	Met	Asp	Gly
				165					170					175	
Asn	Cys	Tyr	Tyr	Lys	Asn	Pro	Cys	Arg	Gln	Ala	Leu	Glu	Val	Ala	Pro
			180					185					190		
Gly	Ala	Leu	Leu	Gly	Leu	Gly	Asn	Leu	Thr	His	Leu	Ser	Leu	Lys	Tyr
		195					200					205			
Asn	Asn	Leu	Thr	Val	Val	Pro	Arg	Asn	Leu	Pro	Ser	Ser	Leu	Glu	Tyr
	210					215					220				
Leu	Leu	Leu	Ser	Tyr	Asn	Arg	Ile	Val	Lys	Leu	Ala	Pro	Glu	Asp	Leu
225					230					235					240
Ala	Asn	Leu	Thr	Ala	Leu	Arg	Val	Leu	Asp	Val	Gly	Gly	Asn	Cys	Arg
				245					250					255	
Arg	Cys	Asp	His	Ala	Pro	Asn	Pro	Cys	Met	Glu	Cys	Pro	Arg	His	Phe
			260					265					270		
Pro	Gln	Leu	His	Pro	Asp	Thr	Phe	Ser	His	Leu	Ser	Arg	Leu	Glu	Gly
		275					280					285			
Leu	Val	Leu	Lys	Asp	Ser	Ser	Leu	Ser	Trp	Leu	Asn	Ala	Ser	Trp	Phe
	290					295					300				
Arg	Gly	Leu	Gly	Asn	Leu	Arg	Val	Leu	Asp	Leu	Ser	Glu	Asn	Phe	Leu
305					310					315					320
Tyr	Lys	Cys	Ile	Thr	Lys	Thr	Lys	Ala	Phe	Gln	Gly	Leu	Thr	Gln	Leu
				325					330					335	
Arg	Lys	Leu	Asn	Leu	Ser	Phe	Asn	Tyr	Gln	Lys	Arg	Val	Ser	Phe	Ala
			340					345					350		
His	Leu	Ser	Leu	Ala	Pro	Ser	Phe	Gly	Ser	Leu	Val	Ala	Leu	Lys	Glu
		355					360					365			
Leu	Asp	Met	His	Gly	Ile	Phe	Phe	Arg	Ser	Leu	Asp	Glu	Thr	Thr	Leu
	370					375					380				
Arg	Pro	Leu	Ala	Arg	Leu	Pro	Met	Leu	Gln	Thr	Leu	Arg	Leu	Gln	Met
385					390					395					400
Asn	Phe	Ile	Asn	Gln	Ala	Gln	Leu	Gly	Ile	Phe	Arg	Ala	Phe	Pro	Gly
				405					410					415	
Leu	Arg	Tyr	Val	Asp	Leu	Ser	Asp	Asn	Arg	Ile	Ser	Gly	Ala	Ser	Glu
			420					425					430		
Leu	Thr	Ala	Thr	Met	Gly	Glu	Ala	Asp	Gly	Gly	Glu	Lys	Val	Trp	Leu

435 440 445
 Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
 450 455 460
 Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
 465 470 475 480
 Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
 485 490 495
 His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
 500 505 510
 Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
 515 520 525
 Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
 530 535 540
 Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
 545 550 555 560
 Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
 565 570 575
 Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
 580 585 590
 Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
 595 600 605
 Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
 610 615 620
 Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
 625 630 635 640
 His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
 645 650 655
 Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
 660 665 670
 Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
 675 680 685
 Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
 690 695 700
 Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
 705 710 715 720
 Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
 725 730 735
 Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
 740 745 750
 Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
 755 760 765
 Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu


```

      770      775      780
Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785      790      795      800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
      805      810      815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
      820      825      830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
      835      840      845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
      850      855      860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865      870      875      880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
      885      890      895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
      900      905      910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
      915      920      925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
      930      935      940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945      950      955      960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
      965      970      975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
      980      985      990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
      995      1000      1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
      1010      1015      1020

Asn Phe Cys Gln Gly Pro Thr Ala Glu
      1025      1030

```

```

<210> 63
<211> 1032
<212> PRT
<213> Homo sapiens

```

```

<400> 63

```

```

Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
1      5      10      15

Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
20      25      30

```

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
 35 40 45
 Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
 50 55 60
 Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
 65 70 75 80
 Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
 85 90 95
 Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
 100 105 110
 Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
 115 120 125
 Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
 130 135 140
 Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
 145 150 155 160
 Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
 165 170 175
 Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
 180 185 190
 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
 195 200 205
 Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
 210 215 220
 Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
 225 230 235 240
 Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255
 Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
 260 265 270
 Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
 275 280 285
 Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
 290 295 300
 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
 305 310 315 320
 Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
 325 330 335
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
 340 345 350
 His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu

355	360	365
Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu		
370	375	380
Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met		
385	390	395
Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly		
	405	410
		415
Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu		
	420	425
		430
Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu		
	435	440
		445
Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu		
	450	455
		460
Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser		
	465	470
		475
Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser		
	485	490
		495
His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val		
	500	505
		510
Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu		
	515	520
		525
Ser His Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu		
	530	535
		540
Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly		
	545	550
		555
Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr		
	565	570
		575
Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser		
	580	585
		590
Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn		
	595	600
		605
Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe		
	610	615
		620
Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu		
	625	630
		635
His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln		
	645	650
		655
Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser		
	660	665
		670
Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Gln		
	675	680
		685
Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg		

690 695 700
 Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
 705 710 715 720

 Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
 725 730 735

 Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
 740 745 750

 Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
 755 760 765

 Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
 770 775 780

 Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
 785 790 795 800

 Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
 805 810 815

 Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
 820 825 830

 Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
 835 840 845

 Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
 850 855 860

 Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
 865 870 875 880

 Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
 885 890 895

 Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
 900 905 910

 Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
 915 920 925

 Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
 930 935 940

 Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
 945 950 955 960

 Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
 965 970 975

 Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
 980 985 990

 Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
 995 1000 1005

 Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
 1010 1015 1020

 Asn Phe Cys Gln Gly Pro Thr Ala Glu

1025 1030
 <210> 64
 <211> 333
 <212> PRT
 <213> Homo sapiens

 <400> 64

 Met Pro Met Lys Trp Ser Gly Trp Arg Trp Ser Trp Gly Pro Ala Thr
 1 5 10 15

 His Thr Ala Leu Pro Pro Pro Gln Gly Phe Cys Arg Ser Ala Leu His
 20 25 30

 Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu Ala
 35 40 45

 Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His Gly
 50 55 60

 Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe Ser
 65 70 75 80

 Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser Asn
 85 90 95

 Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser Leu
 100 105 110

 Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser Pro
 115 120 125

 Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu Ala
 130 135 140

 Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met Thr
 145 150 155 160

 Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His Thr
 165 170 175

 Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala Leu
 180 185 190

 Arg Phe Leu Phe Met Asp Gly Asn Cys Tyr Tyr Lys Asn Pro Cys Arg
 195 200 205

 Gln Ala Leu Glu Val Ala Pro Gly Ala Leu Leu Gly Leu Gly Asn Leu
 210 215 220

 Thr His Leu Ser Leu Lys Tyr Asn Asn Leu Thr Val Val Pro Arg Asn
 225 230 235 240

 Leu Pro Ser Ser Leu Glu Tyr Leu Leu Leu Ser Tyr Asn Arg Ile Val
 245 250 255

 Lys Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu
 260 265 270

 Asp Val Gly Gly Asn Cys Arg Arg Cys Asp His Ala Pro Asn Pro Cys
 275 280 285

Met Glu Cys Pro Arg His Phe Pro Gln Leu His Pro Asp Thr Phe Ser
 290 295 300

His Leu Ser Arg Leu Glu Gly Leu Val Leu Lys Asp Ser Ser Leu Ser
 305 310 315 320

Trp Leu Asn Ala Ser Trp Phe Arg Gly Leu Gly Asn Leu
 325 330

<210> 65

<211> 216

<212> PRT

<213> Homo sapiens

<400> 65

Met Leu Tyr Ser Ser Cys Lys Ser Arg Leu Leu Asp Ser Val Glu Gln
 1 5 10 15

Asp Phe His Leu Glu Ile Ala Lys Lys Gly Phe Cys Arg Ser Ala Leu
 20 25 30

His Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu
 35 40 45

Ala Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His
 50 55 60

Gly Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe
 65 70 75 80

Ser Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser
 85 90 95

Asn Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser
 100 105 110

Leu Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser
 115 120 125

Pro Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu
 130 135 140

Ala Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met
 145 150 155 160

Thr Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His
 165 170 175

Thr Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala
 180 185 190

Leu Arg Phe Leu Phe Met Asp Gly Asn Cys Tyr Tyr Lys Asn Pro Cys
 195 200 205

Arg Gln Ala Leu Glu Val Ala Pro
 210 215

<210> 66

<211> 117
 <212> PRT
 <213> Homo sapiens

<400> 66

```

Met Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala
1           5           10           15

Phe Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp
          20           25           30

Leu Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly
          35           40           45

Asn Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His
          50           55           60

Asp Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys
65           70           75           80

Trp Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His
          85           90           95

Met Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu
          100          105          110

Leu Asn Leu Ser Tyr
          115
  
```

<210> 67
 <211> 1032
 <212> PRT
 <213> Homo sapiens

<400> 67

```

Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
1           5           10           15

Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
          20           25           30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
          35           40           45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
          50           55           60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65           70           75           80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
          85           90           95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
          100          105          110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
          115          120          125
  
```

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
 130 135 140
 Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
 145 150 155 160
 Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
 165 170 175
 Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
 180 185 190
 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
 195 200 205
 Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
 210 215 220
 Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
 225 230 235 240
 Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255
 Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
 260 265 270
 Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
 275 280 285
 Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
 290 295 300
 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
 305 310 315 320
 Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
 325 330 335
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
 340 345 350
 His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
 355 360 365
 Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
 370 375 380
 Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
 385 390 395 400
 Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
 405 410 415
 Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
 420 425 430
 Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
 435 440 445
 Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu

450 455 460
 Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
 465 470 475 480

 Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
 485 490 495

 His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
 500 505 510

 Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
 515 520 525

 Ser His Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
 530 535 540

 Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
 545 550 555 560

 Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
 565 570 575

 Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
 580 585 590

 Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
 595 600 605

 Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
 610 615 620

 Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
 625 630 635 640

 His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
 645 650 655

 Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
 660 665 670

 Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Gln
 675 680 685

 Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
 690 695 700

 Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
 705 710 715 720

 Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
 725 730 735

 Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
 740 745 750

 Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
 755 760 765

 Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
 770 775 780

 Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser

785 790 795 800
 Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
 805 810 815
 Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
 820 825 830
 Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
 835 840 845
 Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
 850 855 860
 Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
 865 870 875 880
 Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
 885 890 895
 Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
 900 905 910
 Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
 915 920 925
 Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
 930 935 940
 Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
 945 950 955 960
 Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
 965 970 975
 Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
 980 985 990
 Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
 995 1000 1005
 Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
 1010 1015 1020
 Asn Phe Cys Gln Gly Pro Thr Ala Glu
 1025 1030

<210> 68

<211> 3200

<212> DNA

<213> murine

<400> 68

tgtcagaggg agcctcggga gaatcctcca tctcccaaca tgggttctccg tcgaaggact 60
 ctgcacccct tgccctcct ggtacaggct gcagtgtctgg ctgagactct ggccttgggt 120
 accctgcctg ccttcctacc ctgtgagctg aagcctcatg gcctggtgga ctgcaattgg 180
 ctgttcctga agtctgtacc ccgtttctct gcggcagcat cctgctccaa catcaccgcg 240
 ctctccttga tctccaaccg tatccaccac ctgcacaact ccgacttcgt ccacctgtcc 300

aacctgcggc agctgaacct caagtggaaac tgtccacca ctggccttag cccctgcac	360
ttctcttgcc acatgacct tgagcccaga accttctgg ctatgcgtac actggaggag	420
ctgaacctga gctataatgg tatcaccact gtgccccgac tgcccagctc cctggtgaat	480
ctgagcctga gccacaccaa catcctgggt tagatgcta acagcctcgc cggcctatac	540
agcctgcgcg ttctcttcat ggacgggaac tgctactaca agaaccctg cacaggagcg	600
gtgaaggatga cccagggcg cctcctgggc ctgagcaatc tcacccatct gtctctgaag	660
tataacaacc tcacaaagggt gcccgcgcaa ctgccccca gcctggagta cctcctgggt	720
tcctataacc tcattgtcaa gctggggcct gaagacctgg ccaatctgac ctcccttcga	780
gtacttgatg tgggtgggaa ttgccgtgc tgcgacctg ccccaatcc ctgtatagaa	840
tgtggccaaa agtccctcca cctgcacct gagaccttc atcacctgag ccatctggaa	900
ggcctgggtgc tgaaggacag ctctctccat aactgaact cttcctgggt ccaaggctg	960
gtcaacctct cgggtgctgga cctaagcgag aactttctct atgaaagcat caaccacacc	1020
aatgcctttc agaacctaac ccgcctgcgc aagctcaacc tgccttcaa ttaccgcaag	1080
aaggatatct ttgccgcct ccacctggca agttccttca agaacctgggt gtcactgcag	1140
gagctgaaca tgaacggcat cttcttccgc tcgctcaaca agtacacgt cagatggctg	1200
gccgatctgc ccaaactcca cactctgcat cttcaaatga acttcatcaa ccaggcacag	1260
ctcagcatct ttggtacctt ccgagccctt cgctttgtgg acttgtcaga caatcgcac	1320
agtgggcctt caacgctgtc agaagccacc cctgaagagg cagatgatgc agagcaggag	1380
gagctgttgt ctgcggatcc tcacccagct ccactgagca cccctgcttc taagaacttc	1440
atggacagggt gtaagaactt caagttcacc atggacctgt ctcggaacaa cctggtgact	1500
atcaagccag agatgtttgt caatctctca cgcctccagt gtcttagcct gagccacaac	1560
tccattgcac aggctgtcaa tggctctcag ttcttgccgc tgactaatct gcagggtgctg	1620
gacctgtccc ataacaaact ggacttgtag cactggaaat cgttcagtga gctaccacag	1680
ttgcaggccc tggacctgag ctacaacagc cagcccttta gcatgaaggg tataggccac	1740
aatttcagtt ttgtggccca tctgtccatg ctacacagcc ttagcctggc acacaatgac	1800
attcataccc gtgtgtcctc acatctcaac agcaactcag tgaggtttct tgacttcagc	1860
ggcaacggta tgggccgcat gtgggatgag gggggccttt atctccattt cttccaaggc	1920
ctgagtggcc tgctgaagct ggacctgtct caaaataacc tgcatatcct ccggccccag	1980
aaccttgaca acctcccaa gagcctgaag ctgctgagcc tccgagacaa ctacctatct	2040
ttctttaact ggaccagtct gtccttcctg cccaacctgg aagtcctaga cctggcaggc	2100
aaccagctaa aggcctgac caatggcacc ctgcctaag gcacctcct ccagaaactg	2160

gatgtcagca gcaacagtat cgtctctgtg gtcccagcct tcttcgctct gccgggtcgag 2220
 ctgaaagagg tcaacctcag ccacaacatt ctcaagacgg tggatcgctc ctggtttggg 2280
 cccattgtga tgaacctgac agttctagac gtgagaagca accctctgca ctgtgcctgt 2340
 ggggcagcct tcgtagactt actgttggag gtgcagacca aggtgcctgg cctggctaata 2400
 ggtgtgaagt gtggcagccc cggccagctg cagggccgta gcatcttcgc acaggacctg 2460
 cggctgtgcc tggatgaggt cctctcttgg gactgctttg gcctttcact ctgggtgtg 2520
 gccgtgggca tgggtgtgcc tatactgcac catctctgcg gctgggacgt ctggtactgt 2580
 tttcatctgt gcctggcatg gctacctttg ctggcccgca gccgacgcag cgcccaagct 2640
 ctcccctatg atgccttcgt ggtgttcgat aaggcacaga gcgcagttgc ggactgggtg 2700
 tataacgagc tgcgggtgcg gctggaggag cggcgcggtc gccgagccct acgcttgtgt 2760
 ctggaggacc gagattggct gcctggccag acgctcttcg agaacctctg ggcttccatc 2820
 tatgggagcc gcaagactct atttgtgtg gcccacacgg accgcgtcag tggcctcctg 2880
 cgcaccagct tcctgctggc tcagcagcgc ctgttgaag accgcaagga cgtggtggtg 2940
 ttggtgatcc tgcgtccgga tgcccaccgc tcccgtatg tgcgactgcg ccagcgtctc 3000
 tgccgccaga gtgtgctctt ctggccccag cagcccaacg ggcagggggg cttctggggc 3060
 cagctgagta cagccctgac tagggacaac cgccacttct ataaccagaa cttctgccgg 3120
 ggacctacag cagaatagct cagagcaaca gctggaaaca gctgcatctt catgcctggt 3180
 tcccagattg ctctgcctgc 3200

<210> 69

<211> 3471

<212> DNA

<213> murine

<400> 69

tgaaagtgtc acttcctcaa ttctctgaga gaccctggtg tggaacatca ttctctgccg 60
 cccagtttgt cagagggagc ctggggagaa tcctccatct cccaacatgg ttctccgtcg 120
 aaggactctg cacccttctg ccctcctggt acaggctgca gtgctggctg agactctggc 180
 cctgggtacc ctgcctgcct tcctaccctg tgagctgaag cctcatggcc tgggtgactg 240
 caattggctg ttctgaagt ctgtaccccg tttctctgcg gcagcatcct gctccaacat 300
 caccgcctc tccttgatct ccaaccgtat ccaccacctg cacaactccg acttcgtcca 360
 cctgtccaac ctgcggcagc tgaacctcaa gtggaactgt ccaccactg gccttagccc 420
 cctgcacttc tcttgccaca tgaccattga gcccagaacc ttcttggtta tgcgtacact 480
 ggaggagctg aacctgagct ataatggtat caccactgtg ccccgactgc ccagctccct 540

ggtgaatctg agcctgagcc acaccaacat cctgggttcta gatgctaaca gcctcgccgg	600
cctatacagc ctgcgcgttc tcttcacatgga cgggaactgc tactacaaga acccctgcac	660
aggagcgggtg aaggtgaccc caggcgccct cctgggcctg agcaatctca cccatctgtc	720
tctgaagtat aacaacctca caaaggtgcc ccgccaactg cccccagcc tggagtacct	780
cctgggtgtcc tataacctca ttgtcaagct ggggcctgaa gacctggcca atctgacctc	840
ccttcgagta cttgatgtgg gtgggaattg ccgtcgctgc gaccatgccc ccaatccctg	900
tatagaatgt ggccaaaagt ccctccacct gcaccctgag accttccatc acctgagcca	960
tctggaaggc ctgggtctga aggacagctc tctccataca ctgaactctt cctgggttcca	1020
aggtctggtc aacctctcgg tgctggacct aagcgagaac tttctctatg aaagcatcaa	1080
ccacaccaat gcctttcaga acctaaccg cctgcgcaag ctcaacctgt ccttcaatta	1140
ccgcaagaag gtatcctttg ccgcctcca cctggcaagt tcttcaaga acctgggtgc	1200
actgcaggag ctgaacatga acggcatctt cttccgctcg ctcaacaagt acacgctcag	1260
atggetggcc gatctgccc aactccacac tctgcatctt caaatgaact tcatcaacca	1320
ggcacagctc agcatctttg gtaccttcg agcccttcgc tttgtggact tgtcagacaa	1380
tcgcatcagt gggccttcaa cgctgtcaga agccaccct gaagaggcag atgatgcaga	1440
gcaggaggag ctgttgtctg cggatcctca ccagctcca ctgagcacc ctgcttctaa	1500
gaacttcattg gacaggtgta agaacttcaa gttcaccatg gacctgtctc ggaacaacct	1560
ggtgactatc aagccagaga tgtttgtcaa tctctcacgc ctccagtgtc ttagcctgag	1620
ccacaactcc attgcacagg ctgtcaatgg ctctcagttc ctgccgctga ctaatctgca	1680
ggtgctggac ctgtcccata acaaactgga cttgtaccac tggaaatcgt tcagttagct	1740
accacagttg caggccctgg acctgagcta caacagccag cccttttagca tgaagggtat	1800
aggccacaat ttcagttttg tgacctatct gtccatgcta cagagcctta gcctggcaca	1860
caatgacatt cataccctg tgctctcaca tctcaacagc aactcagtga ggtttcttga	1920
cttcagcggc aacgggtatg gccgcatgtg ggatgagggg gccctttatc tccatttctt	1980
ccaaggcctg agtggcctgc tgaagctgga cctgtctcaa aataacctgc atatcctccg	2040
gccccagaac cttgacaacc tccccagag cctgaagctg ctgagcctcc gagacaacta	2100
cctatctttc tttaactgga ccagtctgtc ctctctaccc aacctggaag tcctagacct	2160
ggcaggcaac cagctaaagg ccctgaccaa tggcaccctg cctaattggca ccctcctcca	2220
gaaactcgat gtcagtagca acagtatcgt ctctgtggtc ccagccttct tcgctctggc	2280
ggtcgagctg aaagaggtca acctcagcca caacattctc aagacgggtg atcgctcctg	2340
gtttgggccc attgtgatga acctgacagt tctagacgtg agaagcaacc ctctgcactg	2400
tgctgtggg gcagccttcg tagacttact gttggaggtg cagaccaagg tgctggcct	2460

ggctaattggt gtgaagtgtg gcagccccgg ccagctgcag ggccgtagca tcttcgcgca 2520
 ggacctgcgg ctgtgcctgg atgaggtcct ctcttgggac tgctttggcc tttcactctt 2580
 ggctgtggcc gtgggcatgg tggcgcctat actgcacat ctctgcggct gggacgtctg 2640
 gtactgtttt catctgtgcc tggcatggct acctttgctg gcccgcagcc gacgcagcgc 2700
 ccaaactctc ccttatgatg ccttcgtggt gttcgataag gcacagagcg cagttgccga 2760
 ctgggtgtat aacgagctgc ggggtgcggct ggaggagcgg cgcggtcgcc gagccctacg 2820
 cttgtgtctg gaggaccgag attggctgcc tggccagacg ctcttcgaga acctctgggc 2880
 ttccatctat gggagccgca agactctatt tgtgctggcc cacacggacc gcgtcagtgg 2940
 cctcctgcgc accagcttcc tgctggctca gcagcgctg ttggaagacc gcaaggacgt 3000
 ggtggtgttg gtgatcctgc gtccggatgc ccaccgctcc cgctatgtgc gactgcgcca 3060
 gcgtctctgc cgccagagtg tgctcttctg gcccagcag cccaacgggc aggggggctt 3120
 ctgggcccag ctgagtacag ccctgactag ggacaaccgc cacttctata accagaactt 3180
 ctgccgggga cctacagcag aatagctcag agcaacagct ggaaacagct gcatcttcat 3240
 gcctggttcc cgagttgctc tgcctgcctt gctctgtctt actacaccgc tatttgcaa 3300
 gtgcgcaata tatgtacca agccaccagg ccacaggagc aaagggtggc agtaaagggt 3360
 agttttcttc ccatgcatct ttcaggagag tgaagataga caccagacc acacagaaca 3420
 ggactggagt tcattctctg cccctccacc ccactttgcc tgtctctgta t 3471

<210> 70
 <211> 3340
 <212> DNA
 <213> murine

<400> 70
 tctctgagag accctggtgt ggaacatcat tctctgccgc ccagtttgtc agaggagacc 60
 tcgggagaat cctccatctc ccaacatggt tctccgtcga aggactctgc accccttgtc 120
 cctcctggta caggctgcag tgctggctga gactctggcc ctgggtaccc tgctgcctt 180
 cctaccctgt gagctgaagc ctcatggcct ggtggactgc aattggctgt tctgaagtc 240
 tgtaccccggt ttctctcggg cagcatcctg ctccaacatc acccgctctt ccttgatctc 300
 caaccgtatc caccacctgc acaactccga cttcgtccac ctgtccaacc tgcggcagct 360
 gaacctcaag tggaactgtc caccactgg ccttagcccc ctgcacttct cttgccacat 420
 gaccattgag ccagaaacct tcctggctat gcgtacactg gaggagctga acctgagcta 480
 taatggtatc accactgtgc cccgactgcc cagctccctg gtgaatctga gcctgagcca 540
 caccaacatc ctggttctag atgctaacag cctcgccggc ctatacagcc tgcgcgttct 600

cttcatggac gggaaactgct actacaagaa cccctgcaca ggagcgggtga aggtgacccc	660
aggcgccctc ctgggcctga gcaatctcac ccatctgtct ctgaagtata acaacctcac	720
aaaggtgccc cgccaactgc cccccagcct ggagtacctc ctggtgtcct ataacctcat	780
tgtcaagctg gggcctgaag acctggccaa tctgacctcc cttcgagtac ttgatgtggg	840
tgggaattgc cgtcgtgcg accatgcccc caatccctgt atagaatgtg gccaaaagtc	900
cctccacctg caccctgaga ccttccatca cctgagccat ctggaaggcc tgggtgctgaa	960
ggacagctct ctccatacac tgaactcttc ctggttccaa ggtctggtca acctctcggc	1020
gctggacctc agcgagaact ttctctatga aagcatcaac cacaccaatg cctttcagaa	1080
cctaaccgcg ctgcgcaagc tcaacctgtc cttcaattac cgcaagaagg taccctttgc	1140
ccgcctccac ctggcaagtt ccttcaagaa cctggtgtca ctgcaggagc tgaacatgaa	1200
cgcatcttc ttccgctcgc tcaacaagta cacgctcaga tggctggccg atctgcccac	1260
actccacact ctgcatcttc aaatgaactt catcaaccag gcacagctca gcatctttgg	1320
taccttccga gcccttcgct ttgtggactt gtcagacaat cgcctcagtg ggccttcaac	1380
gctgtcagaa gccacccctg aagaggcaga tgatgcagag caggaggagc tgttgtctgc	1440
ggatcctcac ccagctccac tgagcaccac tgcttctaag aacttcatgg acagggtgaa	1500
gaacttcaag ttcaccatgg acctgtctcg gaacaacctg gtgactatca agccagagat	1560
gtttgtcaat ctctcacgac tccagtgtct tagcctgagc cacaactcca ttgcacaggc	1620
tgtcaatggc tctcagttcc tgccgctgac taatctgcag gtgctggacc tgtcccataa	1680
caaactggac ttgtaccact ggaaatcggt cagtgcagta ccacagttgc aggccttgga	1740
cctgggctac aacagccagc ccttttagcat aaaggggtata ggccacaatt tcagttttgt	1800
ggcccatctg tccatgctac acagccttag cctggcacac aatgacattc ataccctgt	1860
gtcctcacat ctcaacagca actcagtgag gtttcttgac ttcagcggca acggtatggg	1920
ccgcatgtgg gatgaggggg gcctttatct ccatttcttc caaggcctga gtggcctgct	1980
gaagctggac ctgtctcaaa ataacctgca taccctccgg cccagaacc ttgacaacct	2040
ccccaaagac ctgaagctgc tgagcctccg agacaactac ctatctttct ttaactggac	2100
cagtctgtcc ttctgcccc acctggaagt cctagacctg gcaggcaacc agctaaaggc	2160
cctgaccaat ggcaccctgc ctaatggcac cctcctccag aaactggatg tcagcagcaa	2220
cagtatcgtc tctgtggtcc cagccttctt cgtctggcg gtcgagctga aagaggtcaa	2280
cctcagccac aacattctca agacgggtgga tcgctcctgg tttgggcccc ttgtgatgaa	2340
cctgacagtt ctagacgtga gaagcaacc tctgcactgt gcctgtgggg cagccttcgt	2400
agacttactg ttggagggtc agaccaaggc gcctggcctg gctaagtgtg tgaagtgtg	2460
cagccccggc cagctgcagg gccgtagcat cttgcacag gacctgcggc tgtgcctgga	2520

tgaggctcctc tcttgggact gctttggcct ttcactcttg gctgtggccg tgggcatggt 2580
 ggtgcctata ctgcaccatc tctgcggctg ggacgtcttg tactgttttc atctgtgcct 2640
 ggcatggcta cctttgctgg ccgcagccg acgcagcgcc caagctctcc cctatgatgc 2700
 cttcgtgggtg ttcgataagg cacagagcgc agttgcggac tgggtgtata acgagctgcg 2760
 ggtgcggctg gaggggaggc gcggtcgccg agccctacgc ttgtgtcttg aggaccgaga 2820
 ttggctgcct ggccagacgc tcttcgagaa cctctgggct tccatctatg ggagccgcaa 2880
 gactctatct gtgtggccc acacggaccg cgtcagtggc ctctgcgca ccagcttcct 2940
 gctggctcag cagcgctgt tggaagaccg caaggacgtg gtggtgttg tgatcctgcg 3000
 tccggatgcc caccgctccc gctatgtgcg actgcgccag cgtctctgcc gccagagtgt 3060
 gctcttttgg cccagcagc ccaacgggca ggggggcttc tgggccagc tgagtacagc 3120
 cctgactagg gacaaccgcc acttctataa ccagaacttc tgccggggac ctacagcaga 3180
 atagctcaga gcaacagctg gaaacagctg catcttcatg cctgggtccc gagttgctct 3240
 gcctgccttg ctctgtctta ctacaccgct atttggcaag tgcgcaatat atgctaccaa 3300
 gccaccgggc ccacggagca aaggttggct gtaaagggtg 3340

<210> 71
 <211> 3471
 <212> DNA
 <213> murine

<400> 71
 tgaaagtgtc acttcctcaa ttctctgaga gaccctgggtg tggaacatca ttctctgccg 60
 cccagtttgt cagagggagc ctcgggagaa tcctccatct cccaacatgg ttctccgtcg 120
 aaggactctg cacccttgt ccctcctggg acaggtgca gtgctggctg agactctggc 180
 cctgggtacc ctgcctgcct tcctaccctg tgagctgaag cctcatggcc tgggtggactg 240
 caattggctg ttctgaagt ctgtaccccg tttctctgcg gcagcatcct gctccaacat 300
 caccgcctc tccttgatct ccaaccgtat ccaccacctg cacaactccg acttcgtcca 360
 cctgtccaac ctgcggcagc tgaacctcaa gtggaactgt ccaccactg gccttagccc 420
 cctgcacttc tcttgccaca tgaccattga gcccagaacc ttcttggtta tgcgtacact 480
 ggaggagctg aacctgagct ataatggtat caccactgtg ccccgactgc ccagctccct 540
 ggtgaatctg agcctgagcc acaccaacat cctgggttcta gatgctaaca gcctcgccgg 600
 cctatacagc ctgcgcgttc tcttcatgga cggaactgc tactacaaga acccctgcac 660
 aggagcgggtg aaggtgaccc caggcgccct cctgggcctg agcaatctca cccatctgtc 720
 tctgaagtat aacaacctca caaaggtgcc ccgccaactg cccccagcc tggagtacct 780

cctggtgtcc tataacctca ttgtcaagct ggggcctgaa gacctggcca atctgacctc	840
ccttcgagta cttgatgtgg gtgggaattg ccgtcgctgc gaccatgccc ccaatccctg	900
tatagaatgt ggccaaaagt ccctccacct gcacctgag accttccatc acctgagcca	960
tctggaaggc ctggtgctga aggacagctc tctccataca ctgaactctt cctggttcca	1020
aggctctggtc aacctctcgg tgctggacct aagcgagaac tttctctatg aaagcatcaa	1080
ccacaccaat gcctttcaga acctaacccg cctgcgcaag ctcaacctgt ccttcaatta	1140
ccgcaagaag gtatcctttg cccgcctcca cctggcaagt tccttcaaga acctggtgtc	1200
actgcaggag ctgaacatga acggcatctt ctccgctcg ctcaacaagt acacgctcag	1260
atggctggcc gatctgccc aactccacac tctgcatctt caaatgaact tcatcaacca	1320
ggcacagctc agcatctttg gtaccttcg agcccttcgc tttgtggact tgtcagacaa	1380
tgcacatcagt gggccttcaa cgctgtcaga agccaccct gaagaggcag atgatgcaga	1440
gcaggaggag ctggtgtctg cggatcctca cccagctcca ctgagcacc ctgcttctaa	1500
gaacttcatg gacaggtgta agaacttcaa gttcaccatg gacctgtctc ggaacaacct	1560
ggtgactatc aagccagaga tgtttgtaa tctctcagc ctccagtgtc ttagcctgag	1620
ccacaactcc attgcacagg ctgtcaatgg ctctcagttc ctgccgctga ctaatctgca	1680
ggtgctggac ctgtcccata acaaactgga cttgtaccac tggaaatcgt tcagtgcagt	1740
accacagttg caggccctgg acctgagcta caacagccag cccttttagca tgaagggat	1800
aggccacaat ttcagttttg tgacctatct gtccatgcta cagagcctta gcctggcaca	1860
caatgacatt cataccctg tgctctcaca tctcaacagc aactcagtga ggtttcttga	1920
cttcagcggc aacggtatgg gccgcatgtg ggatgagggg ggcctttatc tccatttctt	1980
ccaaggcctg agtggcctgc tgaagctgga cctgtctcaa aataacctgc atatcctccg	2040
gccccagaac cttgacaacc tccccagag cctgaagctg ctgagcctcc gagacaacta	2100
cctatctttc tttaactgga ccagtctgtc ctctctaccc aacctggaag tcctagacct	2160
ggcaggcaac cagctaaagg ccctgaccaa tggcaccctg cctaattgga ccctcctcca	2220
gaaactcgat gtcagtagca acagtatcgt ctctgtggtc ccagccttct tcgctctggc	2280
ggtcgagctg aaagaggatca acctcagcca caacattctc aagacgggtg atcgctcctg	2340
gtttggggcc attgtgatga acctgacagt tctagacgtg agaagcaacc ctctgcactg	2400
tgctgtggg gcagccttcg tagacttact gttggagggtg cagaccaagg tgcttggcct	2460
ggctaattgg gtgaagtgtg gcagccccgg ccagctgcag ggccgtagca tcttcgcgca	2520
ggacctgcgg ctgtgcctgg atgaggtcct ctcttgggac tgctttggcc tttcactctt	2580
ggctgtggcc gtgggcatgg tgggtgctat actgcacat ctctgcggct gggacgtctg	2640
gtactgtttt catctgtgcc tggcatggct acctttgctg gcccgagcc gacgcagcgc	2700

```

ccaaactctc ccttatgatg ccttcgtggt gttcgataag gcacagagcg cagttgccga 2760
ctgggtgtat aacgagctgc ggggtgaggct ggaggagcgg cgcggtcgcc gagccctacg 2820
cttgtgtctg gaggaccgag attggctgcc tggccagacg ctcttcgaga acctctgggc 2880
ttccatctat gggagccgca agactctatt tgtgctggcc cacacggacc gcgtcagtg 2940
cctcctgcgc accagcttcc tgctggctca gcagcgctg ttggaagacc gcaaggacgt 3000
ggtggtgttg gtgatcctgc gtccggatgc ccaccgctcc cgctatgtgc gactgcgcca 3060
gcgtctctgc cgccagagtg tgctcttctg gcccagcag cccaacgggc aggggggctt 3120
ctgggcccag ctgagtacag ccctgactag ggacaaccgc cacttctata accagaactt 3180
ctgccgggga cctacagcag aatagctcag agcaacagct ggaaacagct gcattctcat 3240
gcctgggtcc cgagttgctc tgctgcctt gctctgtctt actacaccgc tatttgcaa 3300
gtgcgcaata tatgtacca agccaccagg cccacggagc aaaggttggc agtaaaggg 3360
agttttcttc ccatgcatct ttcaggagag tgaagataga caccagacc acacagaaca 3420
ggactggagt tcattctctg cccctccacc ccactttgcc tgtctctgta t 3471

```

<210> 72
 <211> 1032
 <212> PRT
 <213> murine

<400> 72

```

Met Val Leu Arg Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
1           5           10           15

Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
20           25           30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
35           40           45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
50           55           60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65           70           75           80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
85           90           95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
100          105          110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
115          120          125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
130          135          140

```

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
 145 150 155 160
 Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
 165 170 175
 Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
 180 185 190
 Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
 195 200 205
 Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
 210 215 220
 Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
 225 230 235 240
 Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255
 Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
 260 265 270
 Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
 275 280 285
 Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
 290 295 300
 Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
 305 310 315 320
 Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
 325 330 335
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
 340 345 350
 Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
 355 360 365
 Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
 370 375 380
 Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
 385 390 395 400
 Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
 405 410 415
 Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
 420 425 430
 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
 435 440 445
 Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
 450 455 460
 Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu

465 470 475 480
 Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
 485 490 495

 Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
 500 505 510

 Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
 515 520 525

 Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
 530 535 540

 Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
 545 550 555 560

 Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser
 565 570 575

 Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
 580 585 590

 Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
 595 600 605

 Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
 610 615 620

 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
 625 630 635 640

 Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
 645 650 655

 Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
 660 665 670

 Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
 675 680 685

 Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
 690 695 700

 Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
 705 710 715 720

 Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
 725 730 735

 Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
 740 745 750

 Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
 755 760 765

 Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
 770 775 780

 Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
 785 790 795 800

 Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser

385 390 395 400
 Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
 405 410 415

 Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
 420 425 430

 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
 435 440 445

 Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
 450 455 460

 Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
 465 470 475 480

 Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
 485 490 495

 Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
 500 505 510

 Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
 515 520 525

 Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
 530 535 540

 Leu Pro Gln Leu Gln Ala Leu Asp Leu Gly Tyr Asn Ser Gln Pro Phe
 545 550 555 560

 Ser Ile Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser
 565 570 575

 Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
 580 585 590

 Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
 595 600 605

 Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
 610 615 620

 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
 625 630 635 640

 Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
 645 650 655

 Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
 660 665 670

 Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
 675 680 685

 Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
 690 695 700

 Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
 705 710 715 720

 Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn

```

      725      730      735
Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
      740      745      750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
      755      760      765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
      770      775      780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785      790      795      800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
      805      810      815

Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val
      820      825      830

Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
      835      840      845

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser
      850      855      860

Ala Gln Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865      870      875      880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
      885      890      895

Gly Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp
      900      905      910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
      915      920      925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
      930      935      940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945      950      955      960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
      965      970      975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
      980      985      990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
      995      1000      1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
1010      1015      1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu
1025      1030

```

<210> 74
 <211> 1032
 <212> PRT

<213> murine

<400> 74

```

Met Val Leu Arg Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
1          5          10          15

Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
          20          25          30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
          35          40          45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
          50          55          60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65          70          75          80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
          85          90          95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
          100          105          110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
          115          120          125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
130          135          140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145          150          155          160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
          165          170          175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
          180          185          190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
          195          200          205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
          210          215          220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
225          230          235          240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
          245          250          255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
          260          265          270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
          275          280          285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
          290          295          300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305          310          315          320

```

Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
 325 330 335
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
 340 345 350
 Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
 355 360 365
 Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
 370 375 380
 Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
 385 390 395 400
 Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
 405 410 415
 Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
 420 425 430
 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
 435 440 445
 Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
 450 455 460
 Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
 465 470 475 480
 Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
 485 490 495
 Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
 500 505 510
 Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
 515 520 525
 Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
 530 535 540
 Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
 545 550 555 560
 Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser
 565 570 575
 Met Leu Gln Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
 580 585 590
 Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
 595 600 605
 Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
 610 615 620
 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
 625 630 635 640
 Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu

				645					650					655		
Lys	Leu	Leu	Ser	Leu	Arg	Asp	Asn	Tyr	Leu	Ser	Phe	Phe	Asn	Trp	Thr	
			660					665					670			
Ser	Leu	Ser	Phe	Leu	Pro	Asn	Leu	Glu	Val	Leu	Asp	Leu	Ala	Gly	Asn	
			675				680					685				
Gln	Leu	Lys	Ala	Leu	Thr	Asn	Gly	Thr	Leu	Pro	Asn	Gly	Thr	Leu	Leu	
			690			695					700					
Gln	Lys	Leu	Asp	Val	Ser	Ser	Asn	Ser	Ile	Val	Ser	Val	Val	Pro	Ala	
705					710					715					720	
Phe	Phe	Ala	Leu	Ala	Val	Glu	Leu	Lys	Glu	Val	Asn	Leu	Ser	His	Asn	
				725					730					735		
Ile	Leu	Lys	Thr	Val	Asp	Arg	Ser	Trp	Phe	Gly	Pro	Ile	Val	Met	Asn	
			740					745					750			
Leu	Thr	Val	Leu	Asp	Val	Arg	Ser	Asn	Pro	Leu	His	Cys	Ala	Cys	Gly	
			755				760					765				
Ala	Ala	Phe	Val	Asp	Leu	Leu	Leu	Glu	Val	Gln	Thr	Lys	Val	Pro	Gly	
			770			775					780					
Leu	Ala	Asn	Gly	Val	Lys	Cys	Gly	Ser	Pro	Gly	Gln	Leu	Gln	Gly	Arg	
785					790					795					800	
Ser	Ile	Phe	Ala	Gln	Asp	Leu	Arg	Leu	Cys	Leu	Asp	Glu	Val	Leu	Ser	
				805					810					815		
Trp	Asp	Cys	Phe	Gly	Leu	Ser	Leu	Leu	Ala	Val	Ala	Val	Gly	Met	Val	
			820					825					830			
Val	Pro	Ile	Leu	His	His	Leu	Cys	Gly	Trp	Asp	Val	Trp	Tyr	Cys	Phe	
			835				840					845				
His	Leu	Cys	Leu	Ala	Trp	Leu	Pro	Leu	Leu	Ala	Arg	Ser	Arg	Arg	Ser	
						855					860					
Ala	Gln	Thr	Leu	Pro	Tyr	Asp	Ala	Phe	Val	Val	Phe	Asp	Lys	Ala	Gln	
865					870					875					880	
Ser	Ala	Val	Ala	Asp	Trp	Val	Tyr	Asn	Glu	Leu	Arg	Val	Arg	Leu	Glu	
				885					890					895		
Glu	Arg	Arg	Gly	Arg	Arg	Ala	Leu	Arg	Leu	Cys	Leu	Glu	Asp	Arg	Asp	
			900					905					910			
Trp	Leu	Pro	Gly	Gln	Thr	Leu	Phe	Glu	Asn	Leu	Trp	Ala	Ser	Ile	Tyr	
			915				920					925				
Gly	Ser	Arg	Lys	Thr	Leu	Phe	Val	Leu	Ala	His	Thr	Asp	Arg	Val	Ser	
			930			935					940					
Gly	Leu	Leu	Arg	Thr	Ser	Phe	Leu	Leu	Ala	Gln	Gln	Arg	Leu	Leu	Glu	
945					950					955					960	
Asp	Arg	Lys	Asp	Val	Val	Val	Leu	Val	Ile	Leu	Arg	Pro	Asp	Ala	His	
				965					970					975		
Arg	Ser	Arg	Tyr	Val	Arg	Leu	Arg	Gln	Arg	Leu	Cys	Arg	Gln	Ser	Val	

980 985 990
 Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
 995 1000 1005
 Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
 1010 1015 1020
 Asn Phe Cys Arg Gly Pro Thr Ala Glu
 1025 1030

<210> 75
 <211> 1032
 <212> PRT
 <213> murine

<400> 75

Met Val Leu Arg Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
 1 5 10 15
 Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
 20 25 30
 Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
 35 40 45
 Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
 50 55 60
 Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
 65 70 75 80
 Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
 85 90 95
 Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
 100 105 110
 Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
 115 120 125
 Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
 130 135 140
 Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
 145 150 155 160
 Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
 165 170 175
 Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
 180 185 190
 Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
 195 200 205
 Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
 210 215 220
 Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
 225 230 235 240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255
 Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
 260 265 270
 Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
 275 280 285
 Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
 290 295 300
 Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
 305 310 315 320
 Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
 325 330 335
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
 340 345 350
 Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
 355 360 365
 Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
 370 375 380
 Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
 385 390 395 400
 Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
 405 410 415
 Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
 420 425 430
 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
 435 440 445
 Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
 450 455 460
 Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
 465 470 475 480
 Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
 485 490 495
 Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
 500 505 510
 Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
 515 520 525
 Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
 530 535 540
 Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
 545 550 555 560
 Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser

565 570 575
 Met Leu Gln Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
 580 585 590
 Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
 595 600 605
 Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
 610 615 620
 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
 625 630 635 640
 Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
 645 650 655
 Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
 660 665 670
 Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
 675 680 685
 Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
 690 695 700
 Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
 705 710 715 720
 Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
 725 730 735
 Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
 740 745 750
 Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
 755 760 765
 Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
 770 775 780
 Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
 785 790 795 800
 Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
 805 810 815
 Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val
 820 825 830
 Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
 835 840 845
 His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser
 850 855 860
 Ala Gln Thr Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
 865 870 875 880
 Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
 885 890 895
 Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp

900 905 910
 Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
 915 920 925
 Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
 930 935 940
 Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
 945 950 955 960
 Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
 965 970 975
 Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
 980 985 990
 Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
 995 1000 1005
 Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
 1010 1015 1020
 Asn Phe Cys Arg Gly Pro Thr Ala Glu
 1025 1030

<210> 76
 <211> 3002
 <212> DNA
 <213> Homo sapiens

<400> 76
 gtggcttggg attcactggc aggtttcaga catttagatc tttcttttaa tgactaacac 60
 catgcctatc tgtggagaag ctggcaacat gtcacacctg gaaattgttt ttcaacatta 120
 atactattat ttggcagtaa tccagattgc ttttgccacc aacctgaaga catatagagg 180
 cagaaggaca ggaataattc tatttgtttc ctgttttgaa acttccatct gtaaggctat 240
 caaaaggaga tgtgagagag ggtattgagt ctggcctgac aatgcagttc ttaaaccaaa 300
 ggtccattat gcttctcctc tctgagaatc ctgacttacc tcaacaacgg agacatggca 360
 cagtagccag cttggagact tctcagccaa tgctctgaga tcaagtcgaa gacccaatat 420
 acagggtttt gagctcatct tcatcattca tatgaggaaa taagtggtaa aatccttgga 480
 aatacaatga gactcatcag aaacatttac atattttgta gtattgttat gacagcagag 540
 ggtgatgctc cagagctgcc agaagaaagg gaactgatga ccaactgctc caacatgtct 600
 ctaagaaagg tccccgcaga cttgacccca gccacaacga cactggattt atcctataac 660
 ctcttttttc aactccagag ttcagatttt cattctgtct ccaaactgag agttttgatt 720
 ctatgccata acagaattca acagctggat ctcaaaacct ttgaattcaa caaggagtta 780
 agatatttag atttgtctaa taacagactg aagagtgtaa cttggtattt actggcaggt 840
 ctcagggtatt tagatctttc ttttaatgac tttgacacca tgcctatctg tgaggaagct 900

ggcaacatgt cacacctgga aatcctaggt ttgagtgggg caaaaataca aaaatcagat	960
ttccagaaaa ttgtcatct gcatctaaat actgtcttct taggattcag aactcttcct	1020
cattatgaag aaggtagcct gcccatctta aacacaacaa aactgcacat tgttttacca	1080
atggacacaa atttctgggt tcttttgctg gatggaatca agacttcaaa aatattagaa	1140
atgacaaata tagatggcaa aagccaattt gtaagttagt aaatgcaacg aaatcttagt	1200
ttagaaaatg ctaagacatc ggttctattg cttaataaag ttgatttact ctgggacgac	1260
cttttcctta tcttacaatt tgtttggcat acatcagtg aacactttca gatccgaaat	1320
gtgacttttg gtggttaaggc ttatcttgac cacaattcat ttgactactc aaatactgta	1380
atgagaacta taaaattgga gcatgtacat ttcagagtgt tttacattca acaggataaa	1440
atctatttgc ttttgaccaa aatggacata gaaaacctga caatatcaaa tgcacaaatg	1500
ccacacatgc ttttcccgaa ttatcctacg aaattccaat atttaaattt tgccaataat	1560
atcttaacag acgagttgtt taaaagaact atccaactgc ctcaattgaa aactctcatt	1620
ttgaatggca ataaactgga gacactttct ttagtaagtt gctttgctaa caacacaccc	1680
ttggaacact tggatctgag tcaaaatcta ttacaacata aaaatgatga aaattgctca	1740
tggccagaaa ctgtggtcaa tatgaatctg tcatacaata aattgtctga ttctgtcttc	1800
aggtgcttgc ccaaaagtat tcaaatactt gacctaaata ataaccaaat ccaaactgta	1860
cctaaagaga ctattcatct gatggcctta cgagaactaa atattgcatt taattttcta	1920
actgatctcc ctggatgcag tcatttcagt agactttcag ttctgaacat tgaaatgaac	1980
ttcattctca gcccatctct ggattttgtt cagagctgcc aggaagttaa aactctaaat	2040
gcgggaagaa atccattccg gtgtacctgt gaattaaaaa atttcattca gcttgaaaca	2100
tattcagagg tcattgatgt tggatgggtca gattcataca cctgtgaata ccctttaaac	2160
ctaaggggaa ttaggttaaa agacgttcat ctccacgaat tatcttgcaa cacagctctg	2220
ttgattgtca ccattgtgtt tattatgcta gttctggggg ttgctgtggc cttctgctgt	2280
ctccactttg atctgccctg gtatctcagg atgctaggtc aatgcacaca aacatggcac	2340
agggttagga aaacaacca agaacaactc aagagaaatg tccgattcca cgcatttatt	2400
tcatacagt aacatgattc tctgtgggtg aagaatgaat tgatcccaa tctagagaag	2460
gaagatgggt ctatcttgat ttgcctttat gaaagctact ttgacctgg caaaagcatt	2520
agtgaaaata ttgtaagctt cattgagaaa agctataagt ccatctttgt tttgtctccc	2580
aactttgtcc agaatgagtg gtgccattat gaattttact ttgcccacca caatctcttc	2640
catgaaaatt ctgatcatat aattcttata ttactggaac ccattccatt ctattgcatt	2700
cccaccaggt atcataaact gaaagctctc ctggaaaaaa aagcatactt ggaatggccc	2760
aaggataggg gtaaatgtgg gcttttctgg gcaaaccttc gagctgctat taatgttaat	2820

gtattagcca ccagagaaat gtatgaactg cagacattca cagagttaa tgaagagtct 2880
 cgaggttcta caatctctct gatgagaaca gattgtctat aaaatcccac agtccttggg 2940
 aagttgggga ccacatacac tgttgggatg tacattgata caacctttat gatggcaatt 3000
 tg 3002

<210> 77
 <211> 811
 <212> PRT
 <213> Homo sapiens
 <400> 77

Met Arg Leu Ile Arg Asn Ile Tyr Ile Phe Cys Ser Ile Val Met Thr
 1 5 10 15
 Ala Glu Gly Asp Ala Pro Glu Leu Pro Glu Glu Arg Glu Leu Met Thr
 20 25 30
 Asn Cys Ser Asn Met Ser Leu Arg Lys Val Pro Ala Asp Leu Thr Pro
 35 40 45
 Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln
 50 55 60
 Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys
 65 70 75 80
 His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys
 85 90 95
 Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr
 100 105 110
 Trp Tyr Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp
 115 120 125
 Phe Asp Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu
 130 135 140
 Glu Ile Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln
 145 150 155 160
 Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr
 165 170 175
 Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys
 180 185 190
 Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg
 195 200 205
 Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly
 210 215 220
 Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu
 225 230 235 240

Asn Ala Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp
 245 250 255
 Asp Asp Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu
 260 265 270
 His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp
 275 280 285
 His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu
 290 295 300
 Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr
 305 310 315 320
 Leu Leu Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala
 325 330 335
 Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr
 340 345 350
 Leu Asn Phe Ala Asn Asn Ile Leu Thr Asp Glu Leu Phe Lys Arg Thr
 355 360 365
 Ile Gln Leu Pro His Leu Lys Thr Leu Ile Leu Asn Gly Asn Lys Leu
 370 375 380
 Glu Thr Leu Ser Leu Val Ser Cys Phe Ala Asn Asn Thr Pro Leu Glu
 385 390 395 400
 His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn
 405 410 415
 Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys
 420 425 430
 Leu Ser Asp Ser Val Phe Arg Cys Leu Pro Lys Ser Ile Gln Ile Leu
 435 440 445
 Asp Leu Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His
 450 455 460
 Leu Met Ala Leu Arg Glu Leu Asn Ile Ala Phe Asn Phe Leu Thr Asp
 465 470 475 480
 Leu Pro Gly Cys Ser His Phe Ser Arg Leu Ser Val Leu Asn Ile Glu
 485 490 495
 Met Asn Phe Ile Leu Ser Pro Ser Leu Asp Phe Val Gln Ser Cys Gln
 500 505 510
 Glu Val Lys Thr Leu Asn Ala Gly Arg Asn Pro Phe Arg Cys Thr Cys
 515 520 525
 Glu Leu Lys Asn Phe Ile Gln Leu Glu Thr Tyr Ser Glu Val Met Met
 530 535 540
 Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg
 545 550 555 560
 Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr

565 570 575
 Ala Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu
 580 585 590
 Ala Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg
 595 600 605
 Met Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr
 610 615 620
 Gln Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr
 625 630 635 640
 Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu
 645 650 655
 Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe
 660 665 670
 Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys
 675 680 685
 Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu
 690 695 700
 Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu
 705 710 715 720
 Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr
 725 730 735
 Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys
 740 745 750
 Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp
 755 760 765
 Ala Asn Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu
 770 775 780
 Met Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly
 785 790 795 800
 Ser Thr Ile Ser Leu Met Arg Thr Asp Cys Leu
 805 810

<210> 78
 <211> 2760
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (2529)..(2529)
 <223> n is a, c, g, or t

<400> 78
 aagaatttgg actcatatca agatgctctg aagaagaaca accctttagg atagccactg 60
 caacatcatg accaaagaca aagaacctat tgttaaaagc ttccattttg tttgccttat 120

gatcataata gttggaacca gaatccagtt ctccgacgga aatgaatttg cagtagacaa	180
gtcaaaaaga ggtcttattc atgttccaaa agacctaccg ctgaaaacca aagtcttaga	240
tatgtctcag aactacatcg ctgagcttca ggtctctgac atgagctttc tatcagagtt	300
gacagttttg agactttccc ataacagaat ccagctactt gatttaagtg ttttcaagtt	360
caaccaggat ttagaatatt tggatttatc tcataatcag ttgcaaaaga tatcctgcca	420
tcctattgtg agtttcaggc atttagatct ctcatcatt caatttcaagg ccctgccccat	480
ctgtaaggaa tttggcaact tatcacaact gaatttcttg ggattgagtg ctatgaagct	540
gcaaaaatta gatttgctgc caattgctca cttgcatcta agttatatcc ttctggattt	600
aagaaattat tatataaaag aaaatgagac agaaagtcta caaattctga atgcaaaaac	660
ccttcacctt gtttttcacc caactagttt attcgctatc caagtgaaca tatcagttaa	720
tactttaggg tgcttacaac tgactaatat taaattgaat gatgacaact gtcaagtttt	780
cattaaatth ttatcagaac tcaccagagg tccaacctta ctgaatttta ccctcaacca	840
catagaaacg acttggaat gcctggctcag agtctttcaa tttctttggc ccaaacctgt	900
ggaatatctc aatatttaca atttaacaat aattgaaagc attcgtgaag aagattttac	960
ttattctaaa acgacattga aagcattgac aatagaacat atcacgaacc aagtttttct	1020
gttttcacag acagctttgt acaccgtgtt ttctgagatg aacattatga tgtaaccat	1080
ttcagataca ccttttatac acatgctgtg tcctcatgca ccaagcacat tcaagttttt	1140
gaactttacc cagaacgttt tcacagatag tatttttgaa aaatgttcca cgttagttaa	1200
attggagaca cttatcttac aaaagaatgg attaaaagac cttttcaaag taggtctcat	1260
gacgaaggat atgccttctt tggaaatact ggatgttagc tggaaattctt tggaaatctgg	1320
tagacataaa gaaaactgca cttgggttga gagtatagtg gtgttaaatt tgtcttcaaa	1380
tatgcttact gactctgttt tcagatgttt acctcccagg atcaaggtag ttgatcttca	1440
cagcaataaa ataaagagcg ttccataaca agtcgtaaaa ctggaagctt tgcaagaact	1500
caatgttgct ttcaattctt taactgacct tcctggatgt ggcagcttta gcagcctttc	1560
tgtattgatc attgatcaca attcagtttc ccacctatcg gctgatttct tccagagctg	1620
ccagaagatg aggtcaataa aagcagggga caatccattc caatgtacct gtgagctaag	1680
agaatttgct aaaaatatag accaagtatc aagtgaagtg ttagagggct ggctgatctc	1740
ttataagtgt gactaccag aaagttagat aggaagccca ctaaaggact ttcacatgtc	1800
tgaattatcc tgcaacataa ctctgctgat cgtcaccatc ggtgccacca tgctgggtgtt	1860
ggctgtgact gtgacctccc tctgcatcta cttggatctg ccctggatctc tcaggatggg	1920
gtgccagtgg acccagactc ggccgagggc caggaacata cccttagaag aactccaaag	1980
aaacctccag tttcatgctt ttatttcata tagtgaacat gattctgcct ggtgaaaag	2040

tgaattggta ccttacctag aaaaagaaga tatacagatt tgtcttcatg agaggaactt 2100
 tgtccctggc aagagcattg tggaaaatat catcaactgc attgagaaga gttacaagtc 2160
 catctttgtt ttgtctccca actttgtcca gagtgagtg tgccattacg aactctattt 2220
 tgcccatcac aatctctttc atgaaggatc taataactta atcctcatct tactggaacc 2280
 cattccacag aacagcattc ccaacaagta ccacaagctg aaggctctca tgacgcagcg 2340
 gacttatttg cagtggccca aggagaaaag caaacgtggg ctcttttggg ctaacattag 2400
 agccgctttt aatatgaaat taacactagt cactgaaaac aatgatgtga aatcttaaaa 2460
 aaatttagga aattcaactt aagaaacat tatttacttg gatgatggtg aatagtacag 2520
 tcgtaagtna ctgtctggag gtgcctccat tatcctcatg ccttcaggaa agacttaaca 2580
 aaaacaatgt ttcatctggg gaactgagct aggcggtgag gttagcctgc cagttagaga 2640
 cagcccagtc tcttctgggt taatcattat gtttcaaatt gaaacagtct cttttgagta 2700
 aatgctcagt ttttcagctc ctctccactc tgctttccca aatggattct gttggtgaag 2760

<210> 79
 <211> 2753
 <212> DNA
 <213> Homo sapiens

<400> 79
 agaatttgga ctcatatcaa gatgctctga agaagaacaa cccttttagga tagccactgc 60
 aacatcatga ccaaagacaa agaacctatt gttaaaagct tccattttgt ttgccttatg 120
 atcataatag ttggaaccag aatccagttc tccgacggaa atgaatttgc agtagacaag 180
 tcaaaaagag gtcttattca tgttccaaaa gacctaccgc tgaaaaccaa agtcttagat 240
 atgtctcaga actacatcgc tgagcttcag gtctctgaca tgagctttct atcagagttg 300
 acagttttga gactttccca taacagaatc cagctacttg atttaagtgt tttcaagttc 360
 aaccaggatt tagaatattt ggatttatct cataatcagt tgcaaaagat atcctgccat 420
 cctattgtga gtttcaggca tttagatctc tcattcaatg atttcaaggc cctgcccac 480
 tgtaaggaat ttggcaactt atcacaactg aattttcttg gattgagtgc tatgaagctg 540
 caaaaattag atttgctgcc aattgctcac ttgcatctaa gttatatcct tctggattta 600
 agaaattatt atataaaaga aaatgagaca gaaagtctac aaattctgaa tgcaaaaacc 660
 cttcaccttg tttttcaccc aactagttta ttgcgtatcc aagtgaacat atcagttaat 720
 actttagggt gcttacaact gactaatatt aaattgaatg atgacaactg tcaagttttc 780
 attaaatttt tatcagaact caccagaggt tcaaccttac tgaattttac cctcaaccac 840
 atagaacga cttggaaatg cctggtcaga gtctttcaat ttctttggcc caaacctgtg 900

gaatatctca atatttaca tttacaata attgaaagca ttcgtgaaga agattttact 960
 tattctaaaa cgacattgaa agcattgaca atagaacata tcacgaacca agtttttctg 1020
 ttttcacaga cagctttgta caccgtgttt tctgagatga acattatgat gttaaccatt 1080
 tcagatacac cttttataca catgctgtgt cctcatgcac caagcacatt caagtttttg 1140
 aactttacc agaacgtttt cacagatagt atttttgaaa aatgttccac gttagttaaa 1200
 ttggagacac ttatcttaca aaaaaatgga ttaaaagacc ttttcaaagt aggtctcatg 1260
 acgaaggata tgccttcttt ggaaatactg gatgttagct ggaattcttt ggaatctggt 1320
 agacataaag aaaactgcac ttgggttgag agtatagtgg tgttaaattt gtcttcaaat 1380
 atgcttactg actctgtttt cagatgttta cctcccagga tcaaggtagt tgatcttcac 1440
 agcaataaaa taaagagcgt tcctaaacaa gtcgtaaaac tggaagcttt gcaagaactc 1500
 aatgttgctt tcaattcttt aactgacctt cctggatgtg gcagcttttag cagcctttct 1560
 gtattgatca ttgatcacia ttcagtttcc caccatcgg ctgatttctt ccagagctgc 1620
 cagaagatga ggtcaataaa agcaggggac aatccattcc aatgtacctg tgagctaaga 1680
 gaatttgtca aaaatataga ccaagtatca agtgaagtgt tagagggctg gcctgattct 1740
 tataagtgtg actaccaga aagttataga ggaagcccac taaaggactt tcacatgtct 1800
 gaattatcct gcaacataac tctgctgac gtcaccatcg gtgccaccat gctgggtgtg 1860
 gctgtgactg tgacctcct ctgcatctac ttggatctgc cctggatatct caggatggtg 1920
 tgccagtga cccagactcg gcgcagggcc aggaacatac ccttagaaga actccaaaga 1980
 aacctccagt ttcattgttt tatttcatat agtgaacatg attctgcctg ggtgaaaagt 2040
 gaattggtac cttacctaga aaaagaagat atacagattt gtcttcatga gaggaacttt 2100
 gtccctggca agagcattgt ggaaaatatc atcaactgca ttgagaagag ttacaagtcc 2160
 atctttgttt tgtctcccaa ctttgtccag agtgagtggg gccattacga actctatttt 2220
 gccatcaca atctctttca tgaaggatct aataacttaa tcctcatctt actggaacct 2280
 attccacaga acagcattcc caacaagtac cacaagctga aggtctcat gacgcagcgg 2340
 acttatttgc agtggcccaa ggagaaaagc aaacgtgggc tcttttgggc taacattaga 2400
 gccgctttta atatgaaatt aacactagtc actgaaaaca atgatgtgaa atcttaaaaa 2460
 aatttaggaa attcaactta agaaaccatt atttacttgg atgatggtga atagtacagt 2520
 cgtaagtaac tgtctggagg tgcctccatt atcctcatgc cttcaggaaa gacttaacaa 2580
 aaacaatgtt tcatctgggg aactgagcta ggcggtgagg ttagcctgcc agttagagac 2640
 agcccagtct cttctggttt aatcattatg tttcaaattg aaacagtctc ttttgagtaa 2700
 atgctcagtt tttcagctcc tctccactct gctttcccaa atggattctg ttg 2753

<210> 80
 <211> 796
 <212> PRT
 <213> Homo sapiens

<400> 80

```

Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe Val Cys
1          5          10          15

Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp Gly Asn
          20          25          30

Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
          35          40          45

Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
          50          55          60

Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65          70          75          80

Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
          85          90          95

Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
          100          105          110

Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
          115          120          125

Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
          130          135          140

Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
145          150          155          160

Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
          165          170          175

Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
          180          185          190

Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
          195          200          205

Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
          210          215          220

Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
225          230          235          240

Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe Thr Leu
          245          250          255

Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
          260          265          270

Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
          275          280          285

```

Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
 290 295 300
 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
 305 310 315 320
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
 325 330 335
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
 340 345 350
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
 355 360 365
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
 370 375 380
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
 385 390 395 400
 Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
 405 410 415
 Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
 420 425 430
 Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu
 435 440 445
 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
 450 455 460
 Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
 465 470 475 480
 Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
 485 490 495
 Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
 500 505 510
 Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
 515 520 525
 Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
 530 535 540
 Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
 545 550 555 560
 Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
 565 570 575
 Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
 580 585 590
 Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr
 595 600 605
 Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr

610 615 620
 Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
 625 630 635 640
 Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
 645 650 655
 Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
 660 665 670
 Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
 675 680 685
 Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
 690 695 700
 Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
 705 710 715 720
 His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
 725 730 735
 Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
 740 745 750
 Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
 755 760 765
 Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
 770 775 780
 Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser
 785 790 795

 <210> 81
 <211> 796
 <212> PRT
 <213> Homo sapiens

 <400> 81
 Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe Val Cys
 1 5 10 15
 Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp Gly Asn
 20 25 30
 Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
 35 40 45
 Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
 50 55 60
 Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
 65 70 75 80
 Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
 85 90 95
 Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
 100 105 110

Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
 115 120 125
 Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
 130 135 140
 Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
 145 150 155 160
 Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
 165 170 175
 Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
 180 185 190
 Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
 195 200 205
 Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
 210 215 220
 Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
 225 230 235 240
 Phe Leu Ser Glu Leu Thr Arg Gly Ser Thr Leu Leu Asn Phe Thr Leu
 245 250 255
 Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
 260 265 270
 Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
 275 280 285
 Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
 290 295 300
 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
 305 310 315 320
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
 325 330 335
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
 340 345 350
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
 355 360 365
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
 370 375 380
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
 385 390 395 400
 Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
 405 410 415
 Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
 420 425 430
 Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu

435 440 445
 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
 450 455 460
 Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
 465 470 475 480
 Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
 485 490 495
 Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
 500 505 510
 Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
 515 520 525
 Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
 530 535 540
 Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
 545 550 555 560
 Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
 565 570 575
 Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
 580 585 590
 Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr
 595 600 605
 Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr
 610 615 620
 Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
 625 630 635 640
 Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
 645 650 655
 Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
 660 665 670
 Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
 675 680 685
 Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
 690 695 700
 Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
 705 710 715 720
 His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
 725 730 735
 Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
 740 745 750
 Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
 755 760 765
 Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys

770	775	780
Leu Thr Leu Val Thr	Glu Asn Asn Asp Val Lys	Ser
785	790	795

<210> 82
 <211> 796
 <212> PRT
 <213> Homo sapiens

<400> 82

Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe Val Cys	
1	5 10 15
Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp Gly Asn	
	20 25 30
Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys	
	35 40 45
Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile	
	50 55 60
Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val	
65	70 75 80
Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe	
	85 90 95
Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu	
	100 105 110
Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu	
	115 120 125
Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn	
	130 135 140
Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys	
145	150 155 160
Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu	
	165 170 175
Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln	
	180 185 190
Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu	
	195 200 205
Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln	
	210 215 220
Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys	
225	230 235 240
Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe Thr Leu	
	245 250 255
Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe	
	260 265 270

Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
 275 280 285
 Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
 290 295 300
 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
 305 310 315 320
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
 325 330 335
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
 340 345 350
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
 355 360 365
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
 370 375 380
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
 385 390 395 400
 Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
 405 410 415
 Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
 420 425 430
 Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu
 435 440 445
 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
 450 455 460
 Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
 465 470 475 480
 Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
 485 490 495
 Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
 500 505 510
 Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
 515 520 525
 Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
 530 535 540
 Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
 545 550 555 560
 Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
 565 570 575
 Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
 580 585 590
 Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr

595 600 605
 Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr
 610 615 620
 Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
 625 630 635 640
 Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
 645 650 655
 Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
 660 665 670
 Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
 675 680 685
 Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
 690 695 700
 Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
 705 710 715 720
 His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
 725 730 735
 Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
 740 745 750
 Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
 755 760 765
 Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
 770 775 780
 Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser
 785 790 795

<210> 83
 <211> 2604
 <212> DNA
 <213> murine

<400> 83
 aagtaaaaaat gctgtgaaga atggtaaagt ccctctggga tagcctctgc aacatgagcc 60
 aagacagaaa acccatcgtg gggagtttcc actttgtttg cgccctggcc ttaatagtcg 120
 gaagcatgac ccggttctct aatgaacttg agtctatggt agactattca aacaggaacc 180
 ttactcatgt ccccaaagac ctgccaccaa gaacaaaagc cctgagtctg tctcaaaact 240
 ctatatctga gcttcggatg cctgatatca gctttctgtc agagctgaga gttctgagac 300
 tctcccacaa caggatacgg agccttgatt tccatgtatt cttgttcaat caggacttag 360
 aatacctgga tgtctcacac aatcggttgc aaaacatctc ttgctgccct atggcgagcc 420
 tgaggcatct agacctctca ttcaatgact ttgatgtact gcctgtgtgt aaggaatttg 480
 gcaacctgac gaagctgact ttcctgggat taagtgtgc caagttccga caactggatc 540

tgctcccagt tgctcacttg catctaagct gcattcttct ggacttagtg agtcatcata	600
taaaaggcgg ggaaacagaa agtcttcaga ttcccaatac caccgttctc catttggtct	660
ttcatccaaa tagcttggtc tctgttcaag tgaacatgtc tgtaaacgct ttaggacatt	720
tacaactgag taatattaaa ttgaatgatg aaaactgtca aagggttaatg acatttttat	780
cagaactcac cagaggcca accttattga atgtgaccct ccagcacata gaaacaacct	840
ggaagtgtc ggtaaactt ttccaattct tttggccccg accggtggag tacctcaata	900
tttacaactt aacgataact gagagaatcg acagggaaga atttacttac tcggagacag	960
actgaagtc actgatgata gagcacgtca aaaaccaagt gttcctcttt tcaaaggagg	1020
cgctatactc ggtgtttgct gagatgaaca tcaagatgct ctctatctca gacaccctt	1080
tcatccacat ggtgtgcccg ccatcccaa gctcatttac atttctgaac ttaccaga	1140
atgtttttac tgacagtgtt tttcaaggct gttccacctt aaagagattg cagacactta	1200
tcttaciaag gaatggtttg aagaactttt ttaagtagc tctcatgact aagaatatgt	1260
cctctctgga aactttggat gttagtttga attctttgaa ctctcatgca tatgacagga	1320
catgcgcctg ggctgagagc atattggtgt tgaatttgtc ttcgaatatg cttacaggct	1380
ctgtcttcag atgcttacct cccaaggta aggtccttga ccttcacaac aacaggataa	1440
tgagcatccc taaagatgtc acccacctgc aggttttgca ggaactcaat gtagcatcca	1500
actccttaac tgaccttctt ggggtgtggg ccttcagcag cctttctgtg ctggatcatg	1560
accataactc agtttcccat ccctctgagg atttcttcca gagctgtcag aatattagat	1620
ccctaacagc gggaaacaac ccattccaat gcacatgtga gctgaggac tttgtcaaga	1680
acataggctg ggtagcaaga gaagtgttg agggctggc tgactcttac aggtgtgact	1740
accagaaag ctctaaggga actgcactga gggacttcca catgtctcca ctgtcctgtg	1800
atactgttct gctgactgtc accatcgagg ccactatgct ggtgctggct gtcactggg	1860
ctttcctctg tctctacttt gacctgccct ggtatgtgag gatgctgtgt cagtggacac	1920
agaccaggca cagggccagg cacatccct tagaggaact ccagagaaac ctccagttcc	1980
atgcttttgt ctcatacagt gagcatgatt ctgcctgggt gaagaacgaa ttactacca	2040
acctagagaa agatgacatc cgggtttgcc tccatgagag gaactttgtc cctggcaaga	2100
gcattgtgga gaacatcatc aatttcattg agaagagtta caaggccatc tttgtgctgt	2160
ctccccactt catccagagt gagtgggtgcc attatgaact ctattttgcc catcataatc	2220
tcttccatga aggtctgat aacttaatcc tcatcttgct ggaacccatt ctacagaaca	2280
acattcccag tagataccac aagctgcggg ctctcatggc acagcggact tacttggaat	2340
ggcctactga gaaggcaca cgtgggctgt tttgggcca ccttagagct tcatttatta	2400
tgaagttagc cttagtcaat gaggatgatg tgaaaacttg aaacttgggt ttctaactta	2460

ataaactgtc aacctgggct ctcatgaaca ctgtgggtttt cagttcctac ctggaggtac	2520
ttctgtttgtg gtgtcttagt ttgctctgtg cttatgataa ataacatgtt tagaagtagt	2580
ttatgaagggt gctaagttca ttaa	2604

<210> 84
 <211> 2604
 <212> DNA
 <213> murine

<400> 84	
aagtaaaaat gctgtgaaga atggtaaagt ccctctggga tagcctctgc aacatgagcc	60
aagacagaaa acccatcgtg gggagtttcc actttgtttg cgccctggcc ttaatagtcg	120
gaagcatgac cccgttctct aatgaacttg agtctatggt agactattca aacaggaacc	180
ttactcatgt ccccaaagac ctgccaccaa gaacaaaagc cctgagtctg tctcaaaact	240
ctatatctga gcttcggatg cctgatatca gctttctgtc agagctgaga gttctgagac	300
tctcccacaa caggatacgg agccttgatt tccatgtatt cttgttcaat caggacttag	360
aatacctgga tgtctcacac aatcggttgc aaaacatctc ttgctgccct atggcgagcc	420
tgaggcatct agacctctca ttcaatgact ttgatgtact gcctgtgtgt aaggaatttg	480
gcaacctgac gaagctgact ttctgggat taagtgtgc caagttccga caactggatc	540
tgctcccagt tgctcacttg catctaagct gcattcttct ggacttagtg agtcatcata	600
taaaaggcgg ggaaacagaa agtcttcaga ttcccaatac caccgttctc catttgggtct	660
ttcatccaaa tagcttgttc tctgttcaag tgaacatgtc tgtaaacgct ttaggacatt	720
tacaactgag taatattaaa ttgaatgatg aaaactgtca aaggttaatg acatttttat	780
cagaactcac cagaggtcca accttattga atgtgacctt ccagcacata gaaacaacct	840
ggaagtgtc ggttaaacctt ttccaattct tttggccccg accggtggag tacctcaata	900
tttacaactt aacgataact gagagaatcg acaggaaga atttacttac tcggagacag	960
cactgaagtc actgatgata gagcacgtca aaaaccaagt gttcctcttt tcaaaggagg	1020
cgctatactc ggtgtttgct gagatgaaca tcaagatgct ctctatctca gacaccctt	1080
tcatccacat ggtgtgcccc ccatcccaa gtcatttac atttctgaac tttaccaga	1140
atgtttttac tgacagtgtt tttcaaggct gttccacctt aaagagattg cagacactta	1200
tcttacaag gaatggtttg aagaactttt ttaaagtagc tctcatgact aagaatatgt	1260
cctctctgga aactttggat gttagtttga attctttgaa ctctcatgca tatgacagga	1320
catgcgcctg ggctgagagc atattggtgt tgaatttgtc ttcgaatatg cttacaggct	1380
ctgtcttcag atgcttacct cccaagggtca aggtccttga ccttcacaac aacaggataa	1440

tgagcatccc taaagatgtc acccacctgc aggcttttgca ggaactcaat gtagcatcca	1500
actccttaac tgaccttcct ggggtgtgggg ccttcagcag cctttctgtg ctggcatcg	1560
accataactc agtttcccat ccctctgagg atttcttcca gagctgtcag aatattagat	1620
ccctaacagc gggaaacaac ccattccaat gcacatgtga gctgagggac tttgtcaaga	1680
acataggctg ggtagcaaga gaagtgggtg agggctggcc tgactcttac aggtgtgact	1740
accagaaaag ctctaaggga actgcactga gggacttcca catgtctcca ctgtcctgtg	1800
atactgttct gctgactgtc accatcgggg ccactatgct ggtgctggct gtcactgggg	1860
ctttcctctg tctctacttt gacctgccct ggtatgtgag gatgctgtgt cagtggacac	1920
agaccaggca cagggccagg cacatcccct tagaggaact ccagagaaac ctccagttcc	1980
atgcttttgt ctcatacagt gagcatgatt ctgcctgggt gaagaacgaa ttactacca	2040
acctagagaa agatgacatc cgggtttgcc tccatgagag gaactttgtc cctggcaaga	2100
gcattgtgga gaacatcatc aatttcattg agaagagtta caaggccatc tttgtgctgt	2160
ctcccactt catccagagt gagtgggtgcc attatgaact ctattttgcc catcataatc	2220
tcttccatga aggctctgat aacttaatcc tcatcttgct ggaaccatt ctacagaaca	2280
acattcccag tagataccac aagctgcggg ctctcatggc acagcggact tacttggat	2340
ggcctactga gaagggcaaa cgtgggctgt tttgggcaa ccttagagct tcatttatta	2400
tgaagttagc cttagtcaat gaggatgatg tgaaaacttg aaacttgggt ttctaactta	2460
ataaactgtc aacctgggct ctcatgaaca ctgtggtttt cagttoctac ctggaggtag	2520
ttctgtgtg gtgtcttagt ttgctctgtg cttatgataa ataacatgtt tagaagtagt	2580
ttatgaaggt gctaagttca ttaa	2604

<210> 85
 <211> 2421
 <212> DNA
 <213> murine

<400> 85	
atggtaaagt ccctctggga tagcctctgc aacatgagcc aagacagaaa acccatcgtg	60
gggagtttcc actttgtttg cgccctggcc ttaatagtcg gaagcatgac ccggttctct	120
aatgaacttg agtctatggt agactattca aacaggaacc ttactcatgt ccccaaagac	180
ctgccaccaa gaacaaaagc cctgagtcgt tctcaaaact ctatatctga gcttcggatg	240
cctgatatca gctttctgtc agagctgaga gttctgagac tctccacaa caggatacgg	300
agccttgatt tccatgtatt cttgttcaat caggacttag aatacctgga tgtctcacac	360
aatcggttgc aaaacatctc ttgctgccct atggcgagcc tgaggcatct agacctctca	420
ttcaatgact ttgatgtact gcctgtgtgt aaggaatttg gcaacctgac gaagctgact	480

ttcctgggat taagtgtgc aaagtccga caactggatc tgctcccagt tgctcacttg	540
catctaagct gcattcttct ggacttagtg agttatcata taaaaggcgg ggaaacagaa	600
agtcttcaga ttcccaatac caccgttctc catttgggtct ttcattccaaa tagcttgttc	660
tctgttcaag tgaacatgtc tgtaaacgct ttaggacatt tacaactgag taatattaaa	720
ttgaatgatg aaaactgtca aagggtaatg acatttttat cagaactcac cagaggtcca	780
accttattga atgtgacctt ccagcacata gaaacaacct ggaagtgtc ggttaaactt	840
ttccaatctt tttggccccg accggtggag tacctcaata tttaacaactt aacgataact	900
gagagaatcg acaggaaga atttacttac tcggagacag cactgaagtc actgatgata	960
gagcacgtca aaaaccaagt gttcctcttt tcaaaggagg cgctatactc ggtgtttgct	1020
gagatgaaca tcaagatgct ctctatctca gacaccctt tcatccacat ggtgtgcccc	1080
ccatcccaa gctcatttac atttctgaac ttaccaga atgtttttac tgacagtgtt	1140
tttcaaggct gttccacctt aaagagattg cagacactta tcttacaag gaatggttt	1200
aagaactttt ttaaagtagc tctcatgact aagaatatgt cctctctgga aactttggat	1260
gttagtttga attctttgaa ctctcatgca tatgacagga catgcgcctg ggctgagagc	1320
atattggtgt tgaatttgtc ttogaatatg cttacaggct ctgtcttcag atgcttacct	1380
cccaaggtea aggtccttga ccttcacaac aacaggataa tgagcatccc taaagatgtc	1440
accacctgc aggttttgca ggaactcaat gtagcatcca actccttaac tgaccttct	1500
gggtgtgggg ccttcagcag cctttctgtg ctggtcatcg accataactc agtttcccat	1560
ccctctgagg atttcttcca gagctgtcag aatattagat ccctaacagc gggaaacaac	1620
ccattccaat gcacatgtga gctgaggggac tttgtcaaga acataggctg ggtagcaaga	1680
gaagtgggtg agggctggcc tgactcttac aggtgtgact acccagaaag ctctaaggga	1740
actgcactga gggacttcca catgtctcca ctgtcctgtg atactgttct gctgactgtc	1800
accatcgggg ccactatgct ggtgctggct gtcactgggg ctttctctctg tctctacttt	1860
gacctgccct ggtatgtgag gatgctgtgt cagtggacac agaccaggca cagggccagg	1920
cacatcccct tagaggaact ccagagaaac ctccagttcc atgcttttgt ctcatagct	1980
gagcatgatt ctgcctgggt gaagaacgaa ttactacca acctagagaa agatgacatc	2040
cgggtttgcc tccatgagag gaactttgtc cctggcaaga gcattgtgga gaacatcatc	2100
aatttcattg agaagagtta caaggccatc tttgtgctgt ctccccactt catccagagt	2160
gagtggtgcc attatgaact ctattttgcc catcataatc tcttccatga aggtctgat	2220
aacttaatcc tcatcttgct ggaaccatt ctacagaaca acattoccag tagataccac	2280
aagctgcggg ctctcatggc acagcggact tacttggaat ggcctactga gaagggcaaa	2340
cgtgggctgt tttgggcaa ccttagagct tcatttatta tgaagttagc cttagtcaat	2400

gaggatgatg tgaaaacttg a

2421

<210> 86
 <211> 806
 <212> PRT
 <213> murine

<400> 86

Met	Val	Lys	Ser	Leu	Trp	Asp	Ser	Leu	Cys	Asn	Met	Ser	Gln	Asp	Arg	1	5	10	15
Lys	Pro	Ile	Val	Gly	Ser	Phe	His	Phe	Val	Cys	Ala	Leu	Ala	Leu	Ile	20	25	30	
Val	Gly	Ser	Met	Thr	Pro	Phe	Ser	Asn	Glu	Leu	Glu	Ser	Met	Val	Asp	35	40	45	
Tyr	Ser	Asn	Arg	Asn	Leu	Thr	His	Val	Pro	Lys	Asp	Leu	Pro	Pro	Arg	50	55	60	
Thr	Lys	Ala	Leu	Ser	Leu	Ser	Gln	Asn	Ser	Ile	Ser	Glu	Leu	Arg	Met	65	70	75	80
Pro	Asp	Ile	Ser	Phe	Leu	Ser	Glu	Leu	Arg	Val	Leu	Arg	Leu	Ser	His	85	90	95	
Asn	Arg	Ile	Arg	Ser	Leu	Asp	Phe	His	Val	Phe	Leu	Phe	Asn	Gln	Asp	100	105	110	
Leu	Glu	Tyr	Leu	Asp	Val	Ser	His	Asn	Arg	Leu	Gln	Asn	Ile	Ser	Cys	115	120	125	
Cys	Pro	Met	Ala	Ser	Leu	Arg	His	Leu	Asp	Leu	Ser	Phe	Asn	Asp	Phe	130	135	140	
Asp	Val	Leu	Pro	Val	Cys	Lys	Glu	Phe	Gly	Asn	Leu	Thr	Lys	Leu	Thr	145	150	155	160
Phe	Leu	Gly	Leu	Ser	Ala	Ala	Lys	Phe	Arg	Gln	Leu	Asp	Leu	Leu	Pro	165	170	175	
Val	Ala	His	Leu	His	Leu	Ser	Cys	Ile	Leu	Leu	Asp	Leu	Val	Ser	His	180	185	190	
His	Ile	Lys	Gly	Gly	Glu	Thr	Glu	Ser	Leu	Gln	Ile	Pro	Asn	Thr	Thr	195	200	205	
Val	Leu	His	Leu	Val	Phe	His	Pro	Asn	Ser	Leu	Phe	Ser	Val	Gln	Val	210	215	220	
Asn	Met	Ser	Val	Asn	Ala	Leu	Gly	His	Leu	Gln	Leu	Ser	Asn	Ile	Lys	225	230	235	240
Leu	Asn	Asp	Glu	Asn	Cys	Gln	Arg	Leu	Met	Thr	Phe	Leu	Ser	Glu	Leu	245	250	255	
Thr	Arg	Gly	Pro	Thr	Leu	Leu	Asn	Val	Thr	Leu	Gln	His	Ile	Glu	Thr	260	265	270	

Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro
 275 280 285
 Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp
 290 295 300
 Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile
 305 310 315 320
 Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr
 325 330 335
 Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr
 340 345 350
 Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe
 355 360 365
 Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys
 370 375 380
 Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu
 385 390 395 400
 Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu
 405 410 415
 Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp
 420 425 430
 Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser
 435 440 445
 Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys
 450 455 460
 Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val
 465 470 475 480
 Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu
 485 490 495
 Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val
 500 505 510
 Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser
 515 520 525
 Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys
 530 535 540
 Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg
 545 550 555 560
 Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu
 565 570 575
 Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser
 580 585 590
 Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val

595 600 605
 Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp
 610 615 620
 Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg
 625 630 635 640
 His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
 645 650 655
 Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu
 660 665 670
 Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn
 675 680 685
 Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu
 690 695 700
 Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser
 705 710 715 720
 Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
 725 730 735
 Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln
 740 745 750
 Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln
 755 760 765
 Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe
 770 775 780
 Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn
 785 790 795 800
 Glu Asp Asp Val Lys Thr
 805

<210> 87
 <211> 806
 <212> PRT
 <213> murine

<400> 87

Met Val Lys Ser Leu Trp Asp Ser Leu Cys Asn Met Ser Gln Asp Arg
 1 5 10 15
 Lys Pro Ile Val Gly Ser Phe His Phe Val Cys Ala Leu Ala Leu Ile
 20 25 30
 Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp
 35 40 45
 Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg
 50 55 60
 Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met
 65 70 75 80

Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His
 85 90 95
 Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe Leu Phe Asn Gln Asp
 100 105 110
 Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys
 115 120 125
 Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe
 130 135 140
 Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr
 145 150 155 160
 Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro
 165 170 175
 Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser Tyr
 180 185 190
 His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr
 195 200 205
 Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val
 210 215 220
 Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys
 225 230 235 240
 Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr Phe Leu Ser Glu Leu
 245 250 255
 Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu Gln His Ile Glu Thr
 260 265 270
 Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro
 275 280 285
 Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp
 290 295 300
 Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile
 305 310 315 320
 Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr
 325 330 335
 Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr
 340 345 350
 Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe
 355 360 365
 Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys
 370 375 380
 Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu
 385 390 395 400
 Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu

405 410 415
 Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp
 420 425 430
 Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser
 435 440 445
 Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys
 450 455 460
 Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val
 465 470 475 480
 Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu
 485 490 495
 Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val
 500 505 510
 Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser
 515 520 525
 Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys
 530 535 540
 Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg
 545 550 555 560
 Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu
 565 570 575
 Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser
 580 585 590
 Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val
 595 600 605
 Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp
 610 615 620
 Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg
 625 630 635 640
 His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
 645 650 655
 Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu
 660 665 670
 Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn
 675 680 685
 Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu
 690 695 700
 Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser
 705 710 715 720
 Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
 725 730 735
 Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln

740 745 750
 Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln
 755 760 765
 Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe
 770 775 780
 Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn
 785 790 795 800
 Glu Asp Asp Val Lys Thr
 805

<210> 88
 <211> 806
 <212> PRT
 <213> murine

<400> 88

Met Val Lys Ser Leu Trp Asp Ser Leu Cys Asn Met Ser Gln Asp Arg
 1 5 10 15
 Lys Pro Ile Val Gly Ser Phe His Phe Val Cys Ala Leu Ala Leu Ile
 20 25 30
 Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp
 35 40 45
 Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg
 50 55 60
 Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met
 65 70 75 80
 Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His
 85 90 95
 Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe Leu Phe Asn Gln Asp
 100 105 110
 Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys
 115 120 125
 Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe
 130 135 140
 Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr
 145 150 155 160
 Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro
 165 170 175
 Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser His
 180 185 190
 His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr
 195 200 205
 Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val
 210 215 220

Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys
 225 230 235 240
 Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr Phe Leu Ser Glu Leu
 245 250 255
 Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu Gln His Ile Glu Thr
 260 265 270
 Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro
 275 280 285
 Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp
 290 295 300
 Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile
 305 310 315 320
 Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr
 325 330 335
 Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr
 340 345 350
 Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe
 355 360 365
 Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys
 370 375 380
 Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu
 385 390 395 400
 Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu
 405 410 415
 Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp
 420 425 430
 Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser
 435 440 445
 Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys
 450 455 460
 Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val
 465 470 475 480
 Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu
 485 490 495
 Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val
 500 505 510
 Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser
 515 520 525
 Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys
 530 535 540
 Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg

545 550 555 560
 Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu
 565 570 575

 Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser
 580 585 590

 Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val
 595 600 605

 Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp
 610 615 620

 Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg
 625 630 635 640

 His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
 645 650 655

 Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu
 660 665 670

 Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn
 675 680 685

 Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu
 690 695 700

 Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser
 705 710 715 720

 Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
 725 730 735

 Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln
 740 745 750

 Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln
 755 760 765

 Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe
 770 775 780

 Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn
 785 790 795 800

 Glu Asp Asp Val Lys Thr
 805

<210> 89
 <211> 795
 <212> PRT
 <213> murine

<400> 89

Met Ser Gln Asp Arg Lys Pro Ile Val Gly Ser Phe His Phe Val Cys
 1 5 10 15

 Ala Leu Ala Leu Ile Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu
 20 25 30

Glu Ser Met Val Asp Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys
 35 40 45
 Asp Leu Pro Pro Arg Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile
 50 55 60
 Ser Glu Leu Arg Met Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val
 65 70 75 80
 Leu Arg Leu Ser His Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe
 85 90 95
 Leu Phe Asn Gln Asp Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu
 100 105 110
 Gln Asn Ile Ser Cys Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu
 115 120 125
 Ser Phe Asn Asp Phe Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn
 130 135 140
 Leu Thr Lys Leu Thr Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln
 145 150 155 160
 Leu Asp Leu Leu Pro Val Ala His Leu His Leu Ser Cys Ile Leu Leu
 165 170 175
 Asp Leu Val Ser Tyr His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln
 180 185 190
 Ile Pro Asn Thr Thr Val Leu His Leu Val Phe His Pro Asn Ser Leu
 195 200 205
 Phe Ser Val Gln Val Asn Met Ser Val Asn Ala Leu Gly His Leu Gln
 210 215 220
 Leu Ser Asn Ile Lys Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr
 225 230 235 240
 Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu
 245 250 255
 Gln His Ile Glu Thr Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe
 260 265 270
 Phe Trp Pro Arg Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
 275 280 285
 Thr Glu Arg Ile Asp Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu
 290 295 300
 Lys Ser Leu Met Ile Glu His Val Lys Asn Gln Val Phe Leu Phe Ser
 305 310 315 320
 Lys Glu Ala Leu Tyr Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu
 325 330 335
 Ser Ile Ser Asp Thr Pro Phe Ile His Met Val Cys Pro Pro Ser Pro
 340 345 350
 Ser Ser Phe Thr Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser

```

      355              360              365
Val Phe Gln Gly Cys Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu
  370              375              380

Gln Arg Asn Gly Leu Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys
385              390              395              400

Asn Met Ser Ser Leu Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn
      405              410              415

Ser His Ala Tyr Asp Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val
      420              425              430

Leu Asn Leu Ser Ser Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu
      435              440              445

Pro Pro Lys Val Lys Val Leu Asp Leu His Asn Asn Arg Ile Met Ser
      450              455              460

Ile Pro Lys Asp Val Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val
465              470              475              480

Ala Ser Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser
      485              490              495

Leu Ser Val Leu Val Ile Asp His Asn Ser Val Ser His Pro Ser Glu
      500              505              510

Asp Phe Phe Gln Ser Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn
      515              520              525

Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile
      530              535              540

Gly Trp Val Ala Arg Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg
545              550              555              560

Cys Asp Tyr Pro Glu Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His
      565              570              575

Met Ser Pro Leu Ser Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly
      580              585              590

Ala Thr Met Leu Val Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr
      595              600              605

Phe Asp Leu Pro Trp Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr
      610              615              620

Arg His Arg Ala Arg His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
625              630              635              640

Gln Phe His Ala Phe Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val
      645              650              655

Lys Asn Glu Leu Leu Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys
      660              665              670

Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
      675              680              685

Ile Asn Phe Ile Glu Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro

```

690	695	700
His Phe Ile Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His		
705	710	715 720
His Asn Leu Phe His Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu		
	725	730 735
Glu Pro Ile Leu Gln Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg		
	740	745 750
Ala Leu Met Ala Gln Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly		
	755	760 765
Lys Arg Gly Leu Phe Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys		
	770	775 780
Leu Ala Leu Val Asn Glu Asp Asp Val Lys Thr		
785	790	795

<210> 90
 <211> 10
 <212> DNA
 <213> artificial sequence

<220>

<223> consensus p50 subunit

<220>
 <221> misc_feature
 <222> (7)..(7)
 <223> N = c or t

<400> 90
 ggggatnccc

10

<210> 91
 <211> 10
 <212> DNA
 <213> artificial sequence

<220>

<223> consensus p65 subunit

<220>
 <221> misc_feature
 <222> (4)..(4)
 <223> N = a or g

<220>
 <221> misc_feature
 <222> (5)..(5)
 <223> N = a, c, g, or t

<400> 91
 gggnnntttcc

10

<210> 92

<211> 22
<212> DNA
<213> artificial sequence

<220>

<223> consensus subunit

<400> 92
agttgagggg actttcccag gc 22

<210> 93
<211> 27
<212> DNA
<213> artificial sequence

<220>

<223> CREB binding site

<400> 93
agagattgcc tgacgtcaga gagctag 27

<210> 94
<211> 21
<212> DNA
<213> artificial sequence

<220>

<223> AP-1 binding site

<400> 94
cgcttgatga gtcagccgga a 21

<210> 95
<211> 15
<212> DNA
<213> artificial sequence

<220>

<223> AP-1 binding site

<400> 95
cgcatgagtc agaca 15

<210> 96
<211> 19
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 96

tgcagaagtg aaactgagg 19
<210> . 97
<211> 11
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 97
agaacgaaac a 11

<210> 98
<211> 15
<212> DNA
<213> artificial sequence .

<220>

<223> ISRE

<400> 98
gagaagtgaa agtgg 15

<210> 99
<211> 18
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 99
taagaacatg aaactgaa 18

<210> 100
<211> 15
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 100
atgaaactga aagta 15

<210> 101
<211> 16
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 101
tgaaaaccga aagcgc

16

<210> 102
<211> 13
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 102
agaaatggaa agt

13

<210> 103
<211> 9
<212> DNA
<213> artificial sequence

<220>

<223> SRE

<400> 103
tcacccac

9

<210> 104
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> SRE

<400> 104
ctcacccac

10

<210> 105
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> SRE

<400> 105
gccaccctac

10

<210> 106
<211> 17
<212> DNA
<213> artificial sequence

<220>

<223> NFAT

<400> 106

tatgaaacag tttttcc

17

<210> 107

<211> 9

<212> DNA

<213> artificial sequence

<220>

<223> NFAT

<400> 107

aggaaaactc

9

<210> 108

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> NFAT

<220>

<221> misc_feature

<222> (2)..(2)

<223> N = a or g

<220>

<221> misc_feature

<222> (5)..(5)

<223> N = a or g

<400> 108

anganattcc

10

<210> 109

<211> 16

<212> DNA

<213> artificial sequence

<220>

<223> NFAT

<400> 109

ccagttgagc cagaga

16

<210> 110

<211> 30

<212> DNA

<213> artificial sequence

<220>

<223> GAS

<400> 110

ctttcagttt catattactc taaatccatt

30

<210> 111

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> p53 consensus site

<220>

<221> misc_feature

<222> (1)..(3)

<223> N = a or g

<220>

<221> misc_feature

<222> (5)..(6)

<223> N = a or t

<220>

<221> misc_feature

<222> (8)..(10)

<223> N = c or t

<400> 111

nnncnngnnn

10

<210> 112

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> p53 consensus site

<400> 112

aggcatgcct

10

<210> 113

<211> 10

<212> DNA

<213> artificial sequence

<220>

<223> p53 consensus site

<400> 113

gggcttgccc

10

<210> 114

<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 114
gggcttgctt

10

<210> 115
<211> 13
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 115
gcctggactt gcc

13

<210> 116
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 116
ggacatgccc gggcatgtcc

20

<210> 117
<211> 23
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 117
gtagcattag cccagacatg tcc

23

<210> 118
<211> 36
<212> DNA
<213> artificial sequence

<220>

<223> TARE

<400> 118
gaggtagca gacaagagtc agagtttccc cttgaa

36

<210> 119
 <211> 10
 <212> DNA
 <213> artificial sequence

<220>

<223> SRF

<220>
 <221> misc_feature
 <222> (3)..(8)
 <223> N = a or t

<400> 119
 ccnnnnnnngg 10

<210> 120
 <211> 11
 <212> DNA
 <213> artificial sequence

<220>

<223> SRF

<400> 120
 ccaaataagg c 11

<210> 121
 <211> 670
 <212> DNA
 <213> Homo sapiens

<400> 121
 agaaaaattt taaaaaatta ttcattcata tttttaggag ttttgaatga ttggatatgt 60
 aattatattc atattattaa tgtgtatcta tatagatttt tattttgcat atgtactttg 120
 atacaaaatt tacatgaaca aattacacta aaagttattc cacaaatata cttatcaaatt 180
 taagttaaatt gtcaatagct tttaaactta aatttttagtt taacttttct gtcatttctt 240
 actttgaata aaaagagcaa actttgtagt ttttatctgt gaagtagagg tatacgtaat 300
 atacataaat agatatgcca aatctgtgtt attaaaaatt catgaagatt tcaattagaa 360
 aaaaatacca taaaaggctt tgagtgcagg tgaaaaatag gcaatgatga aaaaaaatga 420
 aaaacttttt aaacacatgt agagagtgcg taaagaaagc aaaaacagag atagaaagta 480
 caactagga atttagaaaa tggaaattag tatgttcact atttaagacc tatgcacaga 540
 gcaagtctt cagaaaacct agaggccgaa gttcaagggt atccatctca agtagcctag 600
 caatatttgc aacatcccaa tggccctgtc cttttcttta ctgatggccg tgctggtgct 660
 cagctacaaa 670

<210> 122
<211> 207
<212> DNA
<213> Homo sapiens

<400> 122
aggttctctg aaggccttgc ttctgcaga tgccttaa at agggaaacata ctgatttcca 60
ctttctta at gcttctggac catttccatt tctgtttttg ctttccttct taactcttta 120
catgagttta gagccgtgtt tctcaa atga tgggctagca cgcgtaagag ctcggtacct 180
atcgatagag aaatgttctg gcacctg 207

<210> 123
<211> 161
<212> DNA
<213> Homo sapiens

<400> 123
aggttctctg aaggcttgc ttctgcaga tgccttaa at agggaaacata ctgatttcca 60
ctttctta at gcttctggac cactttccat ttctgttttt gctttccttc ttgaactctt 120
tacatgagtt tagagccgtg tttctcaacc atttgtttt t 161

<210> 124
<211> 300
<212> DNA
<213> Homo sapiens

<400> 124
ttctcaggtc gtttgctttc ctttgctttc tcccaagtct tgttttacaa tttgctttag 60
tcattcactg aaactttaaa aaacattaga aaacctcaca gtttgtaaat ctttttccct 120
attatatata tcataagata ggagcttaaa taaagagttt tagaaactac taaaatgtaa 180
atgacatagg aaaactgaaa gggagaagtg aaagtgggaa attcctctga atagagagag 240
gaccatctca tataaatagg ccataccac ggagaaagga cattctaact gcaacctttc 300

<210> 125
<211> 401
<212> DNA
<213> Homo sapiens

<400> 125
gatctgta at gaataagcag gaactttgaa gactcagtga ctcagtgagt aataaagact 60
cagtgacttc tgatcctgtc ctaactgcc a ctccttggtg tcccaagaaa gcggttcct 120
gctctctgag gaggacctt tccctggaag gtaaaactaa ggatgtcagc agagaaattt 180
ttccaccatt ggtgcttggc caaagaggaa actgatgagc tcactctaga tgagagagca 240
gtgagggaga gacagagact cgaatttccg gagctatttc agttttcttt tccgttttgt 300

gcaatttcac ttatgatacc ggccaatgct tggttgctat tttggaaact ccccttaggg 360
gatgcccctc aactggccct ataaagggcc agcctgagct g 401

<210> 126
<211> 781
<212> DNA
<213> Homo sapiens

<400> 126
ggttgtctgt atgcctccct gagggtatct cactttctgc tcccatccgc ccctatgagc 60
gagtacctat gagcacagga tgtgcacata tttgagtctt attagtggta cacgcagttt 120
tatcatctcc ccaggtctgt gtctgtatga aatgtgcatg ggtgtgtgtg tgcacgcgtg 180
tgttcccact cggggaatgt ggggagaggt gcatggagcc aagatgggtg gtaaatagta 240
tgtttctgaa attaaaggac taatgtggag gaaggcgccc cagatgtact aaaccctttg 300
ccttcacctc atcctctctg acttgggaag aaccaggatt ttgtttttaa gcccttgggc 360
atacagttgt tccatcccga catgaactca gcctcccgctc tgaccgcccc ttggccttcc 420
ttcttcctcg atctgtggaa cccagggaat ctgcctagtg ctgtctccaa gcaccttggc 480
catgatgtaa acccagagaa attagcatct ccatctcctt ccttattccc caccctttg 540
tcatttcctc ttagttcatt acctgggatt ttgatgtcta tgttcctcc tcgttattga 600
tacacacaca gagagagaca aacaaaaaag gaacttcttg aaattccccc agaaggtttt 660
gagagttgtt ttcaatgttg caacaagtca gtttctagtt taagtttcca tcagaaagga 720
gtagagtata taagttccag taccagcaac agcagcagaa gaaacaacat ctgtttcagg 780
g 781

<210> 127
<211> 277
<212> DNA
<213> Homo sapiens

<400> 127
gcatctccat ctcttctctt attccccacc caaaagtcac ttctcttag ttcatcact 60
gggattttga tgtctatgtt cctcctcgt tattgataca cacacagaga gagacaaaca 120
aaaaaggaac ttcttgaaat tccccagaa ggttttgaga gttgttttca atgttgcaac 180
aagtcagttt ctagtttaag tttccatcag aaaggagtag agtatataag ttccagtacc 240
agcaacagca gcagaagaaa caacatctgt ttcaggg 277

<210> 128
<211> 305
<212> DNA
<213> Homo sapiens

<400> 128

caagacatgc	caagtgtga	gtcactaata	aagaaaaaag	aagtaaagga	agagtgggttc	60
tgcttcttag	cgctagcctc	aatgacgacc	taagctgcac	ttttccccc	agttgtgtct	120
tgcgatgcta	aaggacgtca	ttgcacaatc	ttaataaggt	ttccaatcag	ccccaccgcg	180
tctggcccca	ccctcaccct	ccaacaaaga	tttatcaa	atgtgggatttt	cccatgagtc	240
tcaatattag	agtctcaacc	ccaataaat	ataggactgg	agatgtctct	gaggctcatt	300
ctgcc						305

<210> 129

<211> 1181

<212> DNA

<213> Homo sapiens

<400> 129

cctgcaagag	acaccatcct	gaggggaaga	gggcttctga	accagcttga	ccaataaga	60
aattcttggg	tgccgacggg	gacagcagat	tcagagccta	gagccgtgcc	tgcgctccgta	120
gtttccttct	agcttctttt	tgatttcaaa	tcaagactta	cagggagagg	gagcgataaa	180
cacaaactct	gcaagatgcc	acaaggtcct	cctttgacat	ccccaacaaa	gaaggtgagt	240
agtaatctcc	ccctttctgc	cctgaaccaa	gtggcttcag	taagtttcag	ggctccagga	300
gacctgggca	tgccaggtgcc	gatgaaacag	tggtgaagag	actcagtggc	agtggcagtg	360
gggagagcac	tcgcagcaca	ggcaaacctc	tggcacaaga	gcaaagtcct	cactggagga	420
ttcccaaggg	tcacttggga	gagggcaggc	agcagccaac	ctcctctaag	tgggctgaag	480
caggtgaaga	aatggcagaa	gacgcggtgg	tggcaaaaag	gagtcacaca	ctccacctgg	540
agacgccttg	aagtaactgc	acgaaatttg	agggtgccca	ggcagttcta	caacagccgc	600
ctcacaggga	gagccagaac	acagcaagaa	ctcagatgac	tggtagtatt	accttcttca	660
taatcccagg	cttggggggc	tgcgatggag	tcagaggaaa	ctcagttcag	aacatctttg	720
gtttttacaa	tacaaattaa	ctggaacgct	aaattctagc	ctgttaatct	ggtcactgaa	780
aaaaaaaaaa	tttttttttt	ttcaaaaaac	atagcttttag	cttattttttt	ttttctcttt	840
gtaaaacttc	gtgcatgact	tcagctttac	tcttgtcaag	acatgccaaag	tgctgagtca	900
ctaataaaga	aaaaagaagt	aaaggaagag	tggttctgct	tcttagcgct	agcctcaatg	960
acgacctaa	ctgcactttt	ccccctagtt	gtgtcttgcg	atgctaaagg	acgtcattgc	1020
acaatcttaa	taaggtttcc	aatcagcccc	accgctcttg	gccccaccct	caccctccaa	1080
caaagattta	tcaaagtggg	gattttccca	tgagtctcaa	tattagagtc	tcaaccccca	1140
ataaatatag	gactggagat	gtctctgagg	ctcattctgc	c		1181

<210> 130

<211> 778

<212> DNA

<213> Homo sapiens

<400> 130

```

ctaccacttg tctattctgc tatatagtca gtccttacat tgctttcttc ttctgataga      60
ccaaactctt taaggacaag tacctagtct tatctatttc tagatcccc acattactca      120
gaaagttact ccataaatgt ttgtggaact gatttctatg tgaagacatg tgccccctca      180
ctctgttaac tagcattaga aaaacaaatc ttttgaaaag ttgtagtatg cccctaagag      240
cagtaacagt tcctagaaac tctctaaaat gcttagaaaa agatttattt taaattacct      300
ccccataaaa atgattggct ggcttatctt caccatcatg atagcatctg taattaactg      360
aaaaaaaata attatgccat taaaagaaaa tcatccatga tcttggttcta acacctgcca      420
ctctagtact atatctgtca catggtctat gataaagtta tctagaaata aaaaagcata      480
caattgataa ttcaccaa at tgtggagctt cagtatttta aatgtatatt aaaattaaat      540
tatttttaaag atcaaagaaa actttcgtca tactccgtat ttgataagga acaaatagga      600
agtgtgatga ctcaggtttg ccctgagggg atgggccatc agttgcaaat cgtggaattt      660
cctctgacat aatgaaaaga tgagggtgca taagttctct agtagggtga tgatataaaa      720
agccaccgga gcaactcata aggcacaaac tttcagagac agcagagcac acaagctt      778

```

<210> 131

<211> 207

<212> DNA

<213> Homo sapiens

<400> 131

```

actccgtatt tgataaggaa caaataggaa gtgtgatgac tcaggtttgc cctgagggga      60
tgggccatca gttgcaa atc gtggaatttc ctctgacata atgaaaagat gaggggtgcat      120
aagttctcta gtaggggtgat gatataaaaa gccaccggag cactccataa ggcacaaact      180
ttcagagaca gcagagcaca caagctt                                     207

```

<210> 132

<211> 645

<212> DNA

<213> Homo sapiens

<400> 132

```

gggggtgatt tcactccccg gggctgtccc aggcttgtcc ctgctaccgc caccagcct      60
ttcctgaggc ctcaagcctg ccaccaagcc ccagctcct tctccccgca gggcccaaac      120
acaggcctca ggactcaaca cagcttttcc ctccaacccc gttttctctc cctcaacgga      180
ctcagctttc tgaagccct cccagttcta gttctatctt tttcctgcat cctgtctgga      240
agttagaagg aaacagacca cagacctggt ccccaaaaga aatggaggca ataggttttg      300
aggggcatgg ggacgggggt cagcctccag ggtcctacac acaaatcagt cagtggccca      360

```

gaagaccccc ctcggaatcg gagcagggag gatggggagt gtgaggggta tccttgatgc 420
 ttgtgtgtcc ccaactttcc aaatccccgc ccccgcgatg gagaagaaac cgagacagaa 480
 ggtgcagggc ccactaccgc ttcctccaga tgagctcatg ggtttctcca ccaaggaagt 540
 tttccgctgg ttgaatgatt ctttccccgc cctcctctcg cccagggac atataaaggc 600
 agttgttggc acaccagcc agcagacgct ccctcagcaa ggaca 645

<210> 133
 <211> 457
 <212> DNA
 <213> Homo sapiens

<400> 133
 gcctgtactc agccaagggt gcagagatgt tatatatgat tgctcttcag ggaaccgggc 60
 ctccagctca caccacagct gctcaaccac ctctctctg aattgactgt cccttctttg 120
 gaactctagg cctgacccca ctccctggcc ctcccagccc acgattcccc tgacccgact 180
 ccctttccca gaactcagtc gcctgaaccc ccagcctgtg gttctctcct aggcctcagc 240
 ctttctgccc ttgactgaa acagcagtat cttctaagcc ctgggggctt ccccgggccc 300
 cagccccgac ctagaaccgc cccgctgcct gccacgctgc cactgccgct tcctctataa 360
 agggacctga gcgtccgggc ccaggggctc cgcacagcag gtgaggctct cctgccccat 420
 ctcttggggc tgcccgtgct tcgtgctttg gactacc 457

<210> 134
 <211> 973
 <212> DNA
 <213> Homo sapiens

<400> 134
 gcagcaaadc agaatggcag tttgattcat ggtgctgaga ctggagggtc ctctgctgta 60
 ggctcagaat atgtctaagc aattgaggaa tgtctcagaa aacgtggggc tagtgtgcca 120
 tatttatctg caaagccatt ttccctccct aattctgatt ggataagggc attacagttg 180
 acttagcaaa acctgctggc tgttccctggg gaagtcccat gttgcagact cgaaggattt 240
 atttattgta gcctccaagt tacggaattt ccctctgctc ctcttttttt ggtaatagtg 300
 aattagggtt cactttccaa aacatgaact gtttcttgaa aaaaagaact tcattgcata 360
 tagaaaaaaa caaagggtgc aatccattct aactataatg ctttttctca acacttaaac 420
 ttttacagtt actttcagag gttatttttc aaaatatccc cagtaataga aatttttcat 480
 cttttatagg taaacctaat tttttggtaa cagcaagttg tgcctgatta ttagaacagt 540
 gatttacctg gacagtcctc cttgatcaaa tactataaag taataggact ggctgctttt 600
 gacagggcca aagatctgga actggcaagt tttaaataat tcaataaatg ctttgatcat 660
 tcataacacc attagattaa gtaaatagcc tccaacataa ctattttgag ggaaaacatt 720

gctcatttgg gtatctgatt tgtggtgtgt taaaacaagt ttcacgtctt atagcagtcc 780
ctgaatgaaa acatcataag atggtatcta gaatggtgtg agaaaaggat tcatagctat 840
cctaggggta ttgtaaaaaa caaaggggtgc tttttgagga aatgaattta aaagcggggg 900
ggcacgcata gagacagacc ttgggaaagt agcttgagac agaagggaaa caggttgatt 960
tacgatgggg ttc 973

<210> 135
<211> 333
<212> DNA
<213> Homo sapiens

<400> 135
gctaccttaa gaaggctggt taccatctgg gttttcacag tgctttcaca ttcttatcac 60
tttcaacact actgcaaata ggaagggaca gtaacattta gaagagaaca aaacagaaac 120
tcttggaagc aggaaagggtg catgactcaa agagggaaat tcctgtgccca taaaaggatt 180
gctggtgtat aaaatgctct atatatgccca attatcaatt tcctttcatg ttcagcattt 240
ctactccttc caagaagagc agcaaagctg aagttagcag cagcagcacc agcagcaaca 300
gcaaaaaaca aacatgagtg tgaagggcat ggc 333

<210> 136
<211> 1048
<212> DNA
<213> Homo sapiens

<400> 136
ggtgaccaag aatgtgagca agcccaggca cagccactgt gggcgcctga ccaaacagca 60
ctaaatttgt gtgggacatg atcccagagg tgtgtggctt caccctcaa cgagtggcgt 120
ggcatggagt tactgaatct ccaagggtcaa acaggccctc aaattcatca agaaaagggt 180
agggacaaac atctgtacca agagaaggca ggaggagctg agcaacgtcc tgctgccatg 240
aggaaagcag ctgccaagaa ggactgagcc cctgccatct gcctataatg aaagctttgc 300
aaaataaaat aaatataaaa taaagtaata aaattaaatt aaatttaaaa ataaaataaa 360
gcaaaacaaa ataaaatata taaagtaaaa attgttaaaa tgcaaaacaa tatggacata 420
aatacagaaa cacagggaaa cttcttttagg cactcattta caggtaaaaa tatgaaattg 480
aataaagggtc atctggtgtc aaataatata ggccttatct attataagag tttggactga 540
aaagcaaaag tgagataaca aaaaaaagct tttcagaata ttattttgta tagatatgtg 600
aaggatgaag ggtgggtgaa aggacaaaaa acagaaacac agtcttcctg aatgaatgac 660
aatcagaatt ccgctgcccc aagtagtccg acaattaaat ggatttctag gaaaagctac 720
cttaagaagg ctggttacca tctgggtttt cacagtgcct tcacattctt atcactttca 780

acactactgc aaataggaag ggacagtaac atttagaaga gaacaaaaca gaaactcttg 840
gaagcaggaa aggtgcatga ctcaaagagg gaaattcctg tgccataaaa ggattgctgg 900
tgtataaaat gctctatata tgccaattat caatttcctt tcatgttcag catttctact 960
ccttccaaga agagcagcaa agctgaagtt agcagcagca gcaccagcag caacagcaaa 1020
aaacaaacat gagtgtgaag ggcattggc 1048

<210> 137
<211> 504
<212> DNA
<213> Homo sapiens

<400> 137
agggggcccc gcagcagccc cttggcttcc cttctccctt gcctcccctc cggggctccg 60
gttcagaggc actctgggcg cctgctacag cttccaaact gcgcgccttc cttcttcggc 120
agaaaaggac ttctcagatgc ggcggcgggcg gcggcgggca ctcaggacag cggcccctcc 180
cctaaccggcc gcctctccct ctccccctcg ccgcggcggg ctccccacc tctgggaagg 240
cgctgggggt gtggccaggg accggtataa agtcgggggg agccgggtccc gggcagccgc 300
tcagccccct gccctcgcgc gcccgccgcc tgcctgggcc gggccgagga tgcggcgag 360
cgcctcggcg gccaggcttg ctccctccgg cagcctgct aacttcccc gctacgtccc 420
cgttcgcccg ccggggccgc ccgtctcccc gcgcctccg ggtcgggtcc tccaggagcg 480
ccaggcgctg ccgcctgtg ccct 504

<210> 138
<211> 1042
<212> DNA
<213> Homo sapiens

<400> 138
gatcacaaca gctctacaaa tacacaatga ttacaaggaa tggcgcccca ctggagttgt 60
tcaacgcaaa acttgacat tgcaagtggc aatctcccag gcctgcctcc ctccacgagt 120
gggtctgaat gggcctgaga ggcaaacatc caagaaggag gaagaggctc ggcggcacct 180
ccctccccgg gagttctgct gattccatct tggggaagca gggtaggacca gggcccaaat 240
gcgccttggg gagattgcgg gggcgggaga ggttgcaagg ggcaagtggc aagagcctgt 300
taacgtctta gggcctccag gcctttctgt gcccttagct gtgcctgtac gctttacccc 360
acctcaggag gcttggcttc cagcgggtga ggctggaagc accgggggtgc ggtggaaagg 420
gctctgtcca ggaagaccgg atccgcagag ccgggagtcc gggctaggaa gtccctttct 480
cgggtgggaga ctgaggccgc cttggcgggg cgggacgaga ctctccgag gtcgggaaag 540
ggggccccgc agcagccccct tggcttcctt tctcccttgc ctccccctcg gggctccggt 600

tcagaggcac tctgggcgcc tgctacagct tccaaactgc gccgcttcct tcttcggcag 660
aaaaggactt tcagatgcgg cggcggcgcc ggccggcgact caggacagcg cccctcccc 720
taacggccgc ctctccctct cccctcgcc cgccccggt ccccccacctc tgggaaggcg 780
ctgggggtgt ggccaggac cggtataaag tccgggggag ccggtcccg gcagccgctc 840
agccccctgc ccctcgccgc ccgccgctg cctgggcgg gccgaggatg cggcgcagcg 900
cctcggcgcc caggcttgct ccctccggca cgctgctaa cttccccgc tacgtcccc 960
ttcgccgcc ggccgcccc gtctccccgc gccctccggg tcgggtcctc caggagcgcc 1020
aggcgctgcc gccgtgtgcc ct 1042

<210> 139
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 139
tcgtcgtttt gacgttttgc cggt 24

<210> 140
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 140
tcgtcgtttt gtcgtttttt tcga 24

<210> 141
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 141
tcgtcgtttc gtcgtttcgt cggt 24

<210> 142
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 142

tcgtcgtttc gtcgttttgt cgtt

24

<210> ' 143

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 143

tcgtcgtttt tcggtcgttt t

21

<210> 144

<211> 22

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 144

tcgtcgtttt tcgtgcgttt tt

22

<210> 145

<211> 22

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 145

tcgtcgtttt cggcggccgc cg

22

<210> 146

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 146

tcgtcgtttt acggcgccgt gccg

24

<210> 147

<211> 24

<212> DNA

<213> artificial sequence
<220>

<223> Immunostimulatory nucleic acid

<220>

<221> misc_feature

<222> (2)..(2)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (5)..(5)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (13)..(13)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (21)..(21)

<223> N = 5-methylcytosine

<400> 147

tngtngtttt gtngttttgt ngtt

24

<210> 148

<211> 27

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<220>

<221> misc_feature

<222> (2)..(2)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (5)..(5)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (7)..(7)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (11)..(11)

<223> N = 5-methylcytosine

<220>

<221> misc_feature

<222> (13)..(14)

<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (16)..(16)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (19)..(19)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (22)..(22)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (26)..(27)
<223> N = 5-methylcytosine

<400> 148
tngtngntgt ntngnttnt tnttgnn

27

<210> 149
<211> 21
<212> DNA
<213> artificial sequence

<220>
<223> Immunostimulatory nucleic acid

<220>
<221> misc_feature
<222> (2)..(2)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (8)..(8)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (10)..(10)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (13)..(13)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (16)..(16)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (20)..(20)

<223> N = 5-methylcytosine
<400> 149
gngtttgntn ttnttnttgn g

21

<210> 150
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<220>
<221> misc_feature
<222> (2)..(4)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (8)..(8)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (12)..(12)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (15)..(16)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (19)..(19)
<223> N = 5-methylcytosine

<400> 150
gnnnaagntg gnatnngtna

20

<210> 151
<211> 15
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 151
tcctggcggg gaagt

15

<210> 152
<211> 42
<212> DNA
<213> artificial sequence

<220>

WO 2004/094671

PCT/US2004/012788

<400> 152
gaaactcgag ccaccatgag acagactttg ccttgatatct ac 42

<210> 153
<211> 37
<212> DNA
<213> artificial sequence

<220>

<223> Oligonucleotide

<400> 153
gaaagaattc ttaatgtaca gagtttttgg atccaag 37

<210> 154
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 154
tgctgctttt gtgcttttgt gctt 24

<210> 155
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 155
tccatgacgt tcctgatgct 20

<210> 156
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 156
tccatgagct tcctgatgct 20

<210> 157
<211> 20
<212> DNA
<213> artificial sequence

WO 2004/094671

PCT/US2004/012788

<223> Immunostimulatory nucleic acid

<220>

<221> misc_feature

<222> (8)..(8)

<223> N = 5-methylcytosine

<400> 157

tccatgangt tcctgatgct

20

<210> 158

<211> 22

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 158

tcgtcgtttt cggcgcgcgc cg

22

<210> 159

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 159

ggggacgacg tcgtgggggg g

21

<210> 160

<211> 22

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 160

tgctgctttt cggcggccgc cg

22

<210> 161

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 161

ggggagcagc tgctgggggg g

21